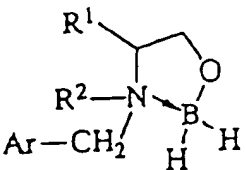




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07F 5/02, C07C 215/28, C07D 207/08, C07C 29/143, C07D 215/14, C07B 53/00, 41/02</p>	A1	<p>(11) International Publication Number: WO 94/17079</p> <p>(43) International Publication Date: 4 August 1994 (04.08.94)</p>
<p>(21) International Application Number: PCT/JP94/00056</p> <p>(22) International Filing Date: 17 January 1994 (17.01.94)</p> <p>(30) Priority Data: 5/7827 20 January 1993 (20.01.93) JP 5/66825 25 March 1993 (25.03.93) JP</p> <p>(71) Applicant (for all designated States except US): NISSAN CHEMICAL INDUSTRIES LTD. [JP/JP]; 7-1, Kanda- Nishiki-cho 3-chome, Chiyoda-ku, Tokyo 101 (JP).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): KASHIHARA, Hiroshi [JP/JP]; Nissan Chemical Industries Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP). SUZUKI, Mikio [JP/JP]; Nissan Chemical Industries Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi- shi, Chiba 274 (JP). OHARA, Yoshio [JP/JP]; Nissan Chemical Industries Ltd., Central Research Institute, 722- 1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP).</p> <p>(74) Agents: YAMAMOTO, Ryoza et al.; Torimoto Kogyo Build- ing, 38, Kanda-Higashimatsushitacho, Chiyoda-ku, Tokyo 101 (JP).</p>		<p>(81) Designated States: AU, CA, CN, CZ, FI, HU, KR, NO, NZ, RO, RU, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report.</p>
<p>(54) Title: OPTICALLY ACTIVE β-AMINOALKOXYBORANE COMPLEX</p> <p>(57) Abstract</p> <p>An optically active β-aminoalkoxyborane complex of formula (I), wherein R¹ is C₁-C₈ alkyl, C₃-C₇ cycloalkyl, C₇-C₁₁ aralkyl or C₆-C₁₀ aryl, R² is hydrogen, C₁-C₈ alkyl, C₃-C₇ cycloalkyl or C₇-C₁₁ aralkyl, or R¹ and R² together form (CH₂)_n wherein n is 3 or 4, and Ar is naphthyl, anthryl or phenanthryl, which may be substituted by from 1 to 3 substituents selected from the group consisting of halogen, nitro, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₁ aralkyl, C₆-C₁₀ aryl, C₁-C₆ alkoxy and styrene polymer substituents.</p> <div style="text-align: center;">  <p>(I)</p> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

DESCRIPTIONTITLE OF THE INVENTIONOPTICALLY ACTIVE β -AMINOALKOXYBORANE COMPLEX

5

TECHNICAL FIELD

The present invention relates to a novel optically active β -aminoalkoxyborane complex and a process for producing an optically active alcohol, wherein the complex is applied as a reducing agent to a carbonyl
10 compound. Particularly, it relates to a process for producing an optically active 1,3-syn-diol compound wherein this borane complex is applied to a 1,3-dicarbonyl compound.

BACKGROUND ART

15 Many physiologically active substances for pharmaceuticals, agricultural chemicals or cosmetics have a 1,2- or 1,3-syn-diol structure. For example, a series of HMG-CoA reductase inhibitors as one type of antihyperlipemia agents have a 1,3-syn-diol as a common
20 partial structure at their mevalonic acid chain moieties, which constitutes an essential structure for developing the reductase inhibitory activities.

Further, among natural physiologically active substances, there are many substances which have a 1,3-
25 syn-diol structure. For example, prostaglandin $Fl\alpha$ and $F2\alpha$ having oxytocic activities or vasopressor activities, pentamycine which is a polyene macrolide antibiotic,

- 2 -

amphotericine B which is a polyene-type antimycotic,
misaquinolide A which is an antitumor macrolide, G-
strophatine which is a cardiac glycoside and pulkerine
which is a sesquiterpene contained in an Indian blanket
5 (Gaillardia pulchella) may be mentioned.

Heretofore, various methods for preparing this 1,3-
syn-diol have been developed by means of chemical
techniques (Tetrahedron Lett., 28, 155 (1987),
Tetrahedron Lett., 26, 2951 (1985)). However, these
10 methods require many steps, since a first chiral center
is introduced and a second chiral center is constructed
based on the first chiral center, and it requires an
extremely low temperature as a reaction condition to
obtain the desired 1,3-syn-diol in high optical yield and
15 at a high syn-selectivity. Thus, they had many
industrial limitations.

Heretofore, a number of methods have been known for
producing an optically active alcohol compound by
asymmetrically reducing a carbonyl compound by means of
20 an optically active reagent. Namely, many methods
including, for example, a method by Corey et al.
employing an optically active borane complex (E. J. Corey
and A. V. Gavai, Tetrahedron Lett., 29, 3201 (1988)), a
Meerwein-Ponndorf-Verley (MPV) type asymmetric reduction
25 method (M. M. Midland, D. C. McDowell and Gabriel, J.
Org. Chem., 54, 159 (1989)) and a method employing an
enzyme or a microorganism (G. Frater, Helv. Chim. Acta,

- 3 -

62, 2815, 2829 (1979) may be mentioned.

For asymmetric reduction of aromatic carbonyl compounds, many reagents showing high selectivity have been developed. However, it has been considered
5 difficult to attain high selectivity for asymmetric reduction of a dialkylcarbonyl even by using these reagents, and it has been possible to attain an asymmetric yield of only 50% at best. Generally, high-electrons of unsaturated groups of aromatic carbonyl
10 compounds are considered to provide substantial effects in a transition state for asymmetric reduction, and for a dialkylcarbonyl with which no such substantial electronic effects can be expected, a reagent is required to have an ability of recognizing the difference in steric effects
15 (Organic Synthetic Chemistry, Vol. 45, No. 2, p. 101 (1987)). Accordingly, in the case of a substrate such as 2-hexanone, no reducing reagent which is capable of sufficiently providing such an ability, has been known. The above-mentioned reagents for asymmetric reduction are
20 all used for asymmetric reduction of monocarbonyl compounds only, and little applications to dicarbonyl compounds have been known.

On the other hand, a method by Yamazaki et al. employing an optically active borane complex is known
25 (Japanese Unexamined Patent Publication No. 146786/1982). Namely, this method is directed to asymmetric reduction of acetophenones by means of an optically active borane

- 4 -

complex prepared from (S)-1-benzyl-2-pyrrolidine methanol and borane. However, the optical purity thereby attainable is only at a level of 69% at the maximum, and it takes a long time of about 60 hours. Thus, this method can hardly be regarded as a practical method. Itsuno et al. have tried asymmetric reduction of a carbonyl compound by a borane complex having a styrene polymer introduced to the benzyl moiety of this (S)-1-benzyl-2-pyrrolidine methanol (S. Itsuno, K. Ito, T. Maruyama, A. Hirao and S. Nakahama, *Bul. Chem. Soc. Jpn.*, 59, 3329 (1986)), but have failed to attain a satisfactory optical purity. Both the Yamazaki et al. method and the Itsuno et al. method have been used for reduction of monocarbonyl compounds and have not been utilized for reduction of dicarbonyl compounds. As an application to dicarbonyl compounds, a method by Noyori et al. employing a BINAP-Ru complex (Ryoji Noyori and Hidemasa Takaya, *Chemistry*, 43, 146 (1988) and R. Noyori, *Chem. Soc. Rev.*, 18, 187 (1988)) is known, and this method is applied also to direct reduction of 1,2-dicarbonyl and 1,3-dicarbonyl compounds. In any case, however, the resulting optically active diols are of anti-form.

According to a recent method by Hiyama et al. for direct asymmetric reduction of 1,3-dicarbonyl compounds having asymmetric ester groups introduced thereto (European Patent No. 475627) or an asymmetric reduction

- 5 -

method of 1,3-dicarbonyl compounds employing an optically active borane reagent (Tetrahedron Lett., 29, 6467 (1988)), 1,3-syn-diol compounds are obtainable by the intended syn-selective asymmetric reduction, but no
5 adequate results have been obtained with respect to the asymmetric yield. Thus, a process for direct reduction of dicarbonyl compounds to obtain optically active syn-diol compounds, has not yet been established.

DISCLOSURE OF INVENTION

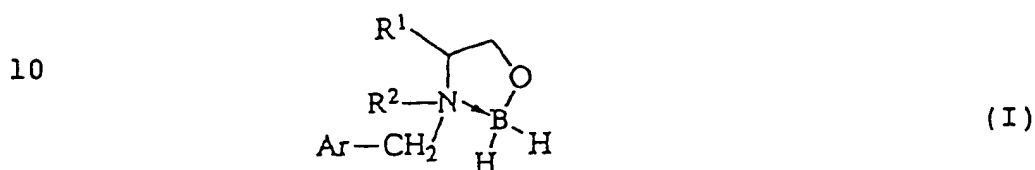
10 It is an object of the present invention to obtain an optically active alcohol in good asymmetric yield by asymmetric reduction of a carbonyl compound, particularly to obtain an optically active 1,3-syn-diol compound in good asymmetric yield at a high syn-forming rate by
15 simultaneously reducing two carbonyl groups of a dicarbonyl compound, and to provide an excellent reducing catalyst capable of realizing the object and to provide an optically active 1,3-syn-diol compound by using such a catalyst.

20 The present inventors have conducted extensive studies with an aim to develop a reducing reagent capable of providing a high asymmetric yield and a high syn-selectivity and useful under a wide range of reaction conditions and a process for producing an optically
25 active 1,3-syn-diol compound, and as a result, have found it possible to produce an optically active 1,3-syn-diol compound in the maximum asymmetric yield of 100%ee and at

- 6 -

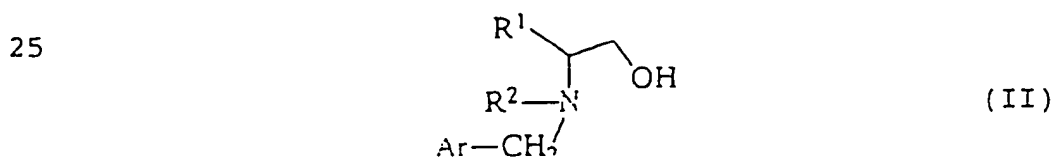
a high syn-selectivity of 99% by reducing a 1,3-dicarbonyl compound by means of an optically active β -(N-naphthylmethyl)aminoalkoxyborane complex prepared from an optically active β -(N-naphthylmethyl)aminoalcohol compound and borane. The present invention has been accomplished on the basis of this discovery.

Thus, the present invention provides an optically active β -aminoalkoxyborane complex of the formula (I):



wherein R^1 is C_1-C_8 alkyl, C_3-C_7 cycloalkyl, C_7-C_{11} aralkyl or C_6-C_{10} aryl, R^2 is hydrogen, C_1-C_8 alkyl, C_3-C_7 cycloalkyl or C_7-C_{11} aralkyl, or R^1 and R^2 together form $(CH_2)_n$ wherein n is 3 or 4, and Ar is naphthyl, anthryl or phenanthryl, which may be substituted by from 1 to 3 substituents selected from the group consisting of halogen, nitro, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{11} aralkyl, C_6-C_{10} aryl, C_1-C_6 alkoxy and styrene polymer substituents.

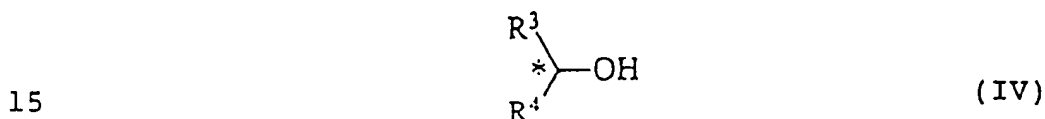
The present invention also provides an optically active β -aminoalcohol compound of the formula (II):



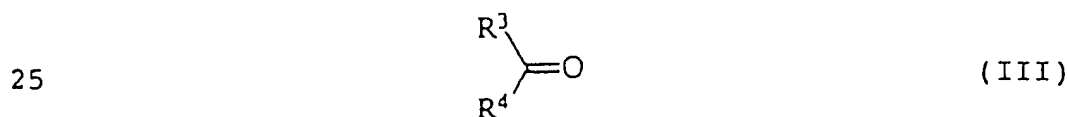
- 7 -

wherein R^1 is C_1-C_8 alkyl, C_3-C_7 cycloalkyl, C_7-C_{11} aralkyl or C_6-C_{10} aryl, R^2 is hydrogen, C_1-C_8 alkyl or C_7-C_{11} aralkyl, or R^1 and R^2 together form $(CH_2)_n$ wherein n is 3 or 4, and Ar is naphthyl, anthryl or phenanthryl, which may be substituted by from 1 to 3 substituents selected from the group consisting of halogen, nitro, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{11} aralkyl, C_6-C_{10} aryl, C_1-C_6 alkoxy and styrene polymer substituents.

Further, the present invention provides a process for producing an optically active alcohol compound of the formula (IV):



wherein R^3 and R^4 differ from each other and represent C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkenyl, C_7-C_{11} aralkyl, and C_6-C_{14} aryl, or R^3 and R^4 together form a cyclic structure, and * indicates an optically active center, which comprises reducing a carbonyl compound of the formula (III):



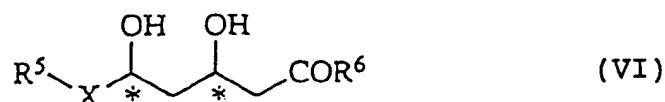
wherein R^3 and R^4 are as defined above, with the

- 8 -

optically active β -aminoalkoxyborane complex as defined above.

Furthermore, the present invention provides a process for producing a compound of the formula (VI).

5

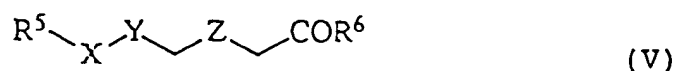


wherein when X is a bond, R⁵ is CHO, CH(OR⁹)(OR¹⁰)
 10 (wherein each of R⁹ and R¹⁰ which are independent of each other, is hydrogen or C₁-C₃ alkyl, or R⁹ and R¹⁰ together form C₂-C₅ alkylene), CH₂OR¹¹ (wherein R¹¹ is hydrogen, C₁-C₃ alkyl, benzyl which may be substituted by methyl or methoxy, trityl, tetrahydropyranyl, methoxymethyl,
 15 trimethylsilyl, dimethyl-tert-butylsilyl or diphenyl-tert-butylsilyl), CH₂R¹² (wherein R¹² is fluoro, chloro, bromo or iodo), CN, CO₂R¹³ (wherein R¹³ is hydrogen, C₁-C₄ alkyl, or benzyl which may be substituted by methyl or methoxy), or CONR¹⁴R¹⁵ (wherein each of R¹⁴ and R¹⁵ which
 20 are independent of each other, is hydrogen, C₁-C₃ alkyl, benzyl, 1-methylbenzyl, or phenyl which may be substituted by methyl or methoxy), and when X is -CH₂-, -CH₂CH₂-, -CH=CH-, -(CH₃)C=CH-, -CH=C(CH₃)- or -C≡C-, R⁵ is hydrogen, trialkylsilyl, a carbon ring aliphatic
 25 group, a carbon ring aromatic group, a heterocyclic aromatic group, a condensed heterocyclic aromatic group, a chain unsaturated aliphatic group or a cyclic

- 9 -

unsaturated aliphatic group, and R^6 is hydroxyl, C_1 - C_{10} alkoxy, OM (wherein M is lithium, sodium, potassium, calcium, NHR'_3 (wherein R' is hydrogen, C_1 - C_3 alkyl, C_3 - C_7 cycloalkyl, C_2 - C_5 alkenyl, phenyl or benzyl)) or C_0 - C_7 amino, and * is an optically active center, provided that the two optically active centers take a syn conformation to each other, which comprises reducing a carbonyl compound of the formula (V):

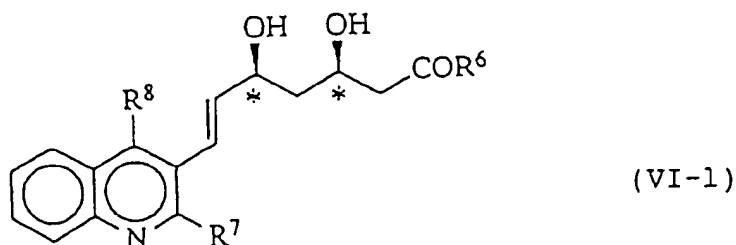
10



wherein R^5 , R^6 and X are as defined above, and each of Y and Z which are independent of each other, is $-CO-$ or $-CH(OH)-$, provided that Y and Z are not simultaneously $-CH(OH)-$, with the optically active β -aminoalkoxyborane complex as defined above.

Still further, the present invention provides a process for producing a compound of the formula (VI-1):

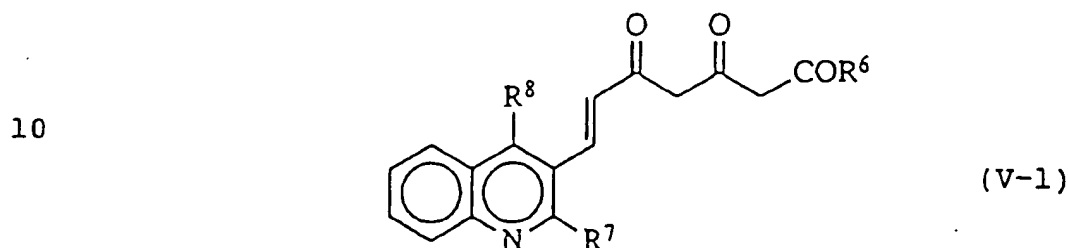
20



wherein R^6 is hydroxyl, C_1 - C_{10} alkoxy, OM (wherein M is lithium, sodium, potassium, calcium, NHR'_3 (wherein R' is hydrogen, C_1 - C_3 alkyl, C_3 - C_7 cycloalkyl, C_2 - C_5 alkenyl,

- 10 -

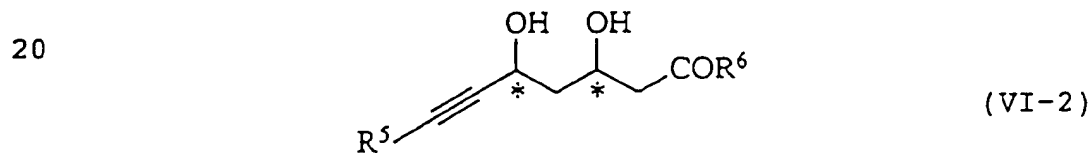
phenyl or benzyl)) or C₀-C₇ amino, R⁷ is C₁-C₇ alkyl or C₃-C₇ cycloalkyl, R⁸ is phenyl which may be substituted by C₁-C₇ alkyl, fluoro, chloro or bromo, * indicates an optically active center, provided that the two optically active centers take a syn conformation to each other, which comprises reducing a 1,3-dicarbonyl compound of the formula (V-1):



wherein R⁶, R⁷ and R⁸ are as defined above, with the optically active β-aminoalkoxyborane complex as defined above.

15

Furthermore, the present invention provides a process for producing an optically active 1,3-syn-diol compound of the formula (VI-2):



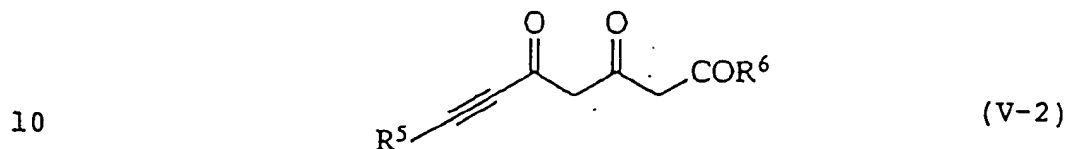
wherein R⁵ is hydrogen, trialkylsilyl, a carbon ring aliphatic group, a carbon ring aromatic group, a heterocyclic aromatic group, a condensed heterocyclic aromatic group, a chain unsaturated aliphatic group or a cyclic unsaturated aliphatic group, R⁶ is hydroxyl, C₁-

25

- 11 -

C₁₀ alkoxy, OM (wherein M is lithium, sodium, potassium, calcium, NHR'₃ (wherein R' is hydrogen, C₁-C₃ alkyl, C₃-C₇ cycloalkyl, C₂-C₅ alkenyl, phenyl or benzyl)) or C₀-C₇ amino, and * indicates an optically active center,

5 provided that the two optically active centers take a syn conformation to each other, which comprises reducing a 1,3-dicarbonyl compound of the formula (V-2):



wherein R⁵ and R⁶ are as defined above, with the optically active β-aminoalkoxyborane complex as defined above.

15 In this specification, n represents normal, i iso, sec secondary, tert tertiary, Me methyl, Et ethyl, Bu butyl, Ph phenyl, and THF tetrahydrofuran.

BEST MODE FOR CARRYING OUT THE INVENTION

Now, the compounds of the present invention will be
20 described in detail. The following substituents may be mentioned as substituents for R¹ of each of the formulas (I) and (II).

C₁-C₈ alkyl includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl,
25 butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl.

C₃-C₇ cycloalkyl includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

- 12 -

C₇-C₁₁ aralkyl includes, for example, benzyl, o-methylbenzyl, m-methylbenzyl, p-methylbenzyl, p-chlorobenzyl, 1-methylbenzyl, phenethyl, o-methylphenethyl, m-methylphenethyl, p-methylphenethyl, 3-phenylpropyl, 3-(o-methylphenyl)propyl, 3-(m-methylphenyl)propyl, 3-(p-methylphenyl)propyl, 4-phenylbutyl, α -naphthylmethyl and β -naphthylmethyl.

C₆-C₁₀ aryl includes, for example, phenyl, o-tolyl, m-tolyl, p-tolyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethylphenyl, 2,3,6-trimethylphenyl, 3,4,5-trimethylphenyl, 3,4,6-trimethylphenyl, 2,4,6-trimethylphenyl, α -naphthyl and β -naphthyl.

C₁-C₈ alkyl, C₃-C₇ cycloalkyl and C₇-C₁₁ aralkyl as substituents for R² are the same as the corresponding substituents for R¹.

Ar is naphthyl, anthryl or phenanthryl, which may optionally be substituted by from 1 to 3 substituents selected from the group consisting of halogen, nitro, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₁ aralkyl, C₆-C₁₀ aryl, C₁-C₆ alkoxy and styrene polymer substituents. The respective substituents will be described below.

Halogen includes fluorine, chlorine, bromine and iodine.

- 13 -

C₁-C₆ alkyl includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl.

C₃-C₇ cycloalkyl is the same as the corresponding
5 substituent for R¹.

C₂-C₆ alkenyl includes, for example, vinyl, 2-propenyl, 3-butenyl, 4-pentenyl and 5-hexenyl.

C₂-C₆ alkynyl includes, for example, ethynyl, 2-propynyl, 3-butynyl, 4-pentynyl and 5-hexynyl.

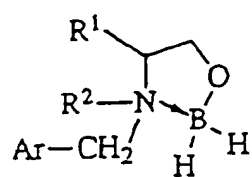
10 C₁-C₆ alkoxy includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy, tert-butoxy, n-pentoxy and n-hexoxy.

The compounds of the formulas (I) and (II) of the present invention include, for example, compounds
15 presented in Table 1. However, it should be understood that the compounds of the present invention are not restricted to such specific examples. Here, Me represents a methyl group, t-Bu a tertiary butyl group, and Ph a phenyl group.

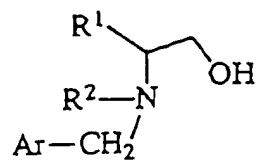
20

25

Table 1



(I)



(II)

R ¹	R ²	Ar
CH ₃	CH ₃	
CH ₃	t-Bu	
CH ₃		
CH ₃		
CH ₃		
CH ₃	CH ₃	

Table 1 (continued)

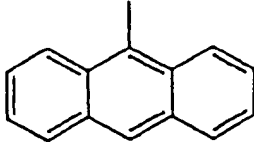
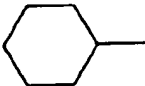
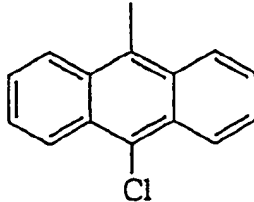
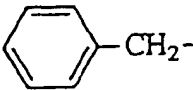
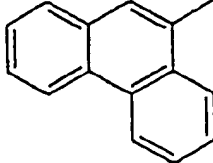
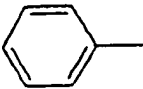
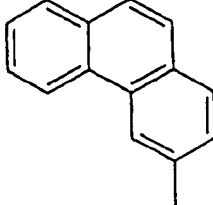
R^1	R^2	Ar
CH_3	t-Bu	
CH_3		
CH_3		
CH_3		

Table 1 (continued)

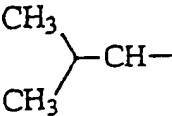
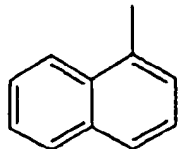
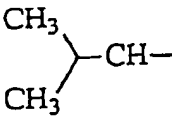
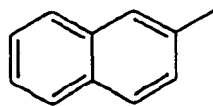
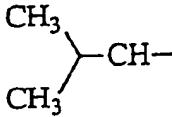
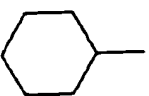
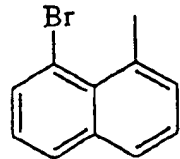
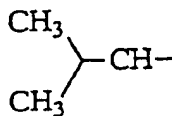
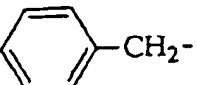
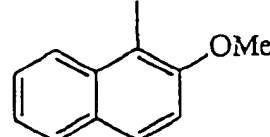
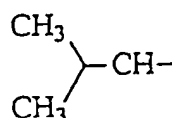
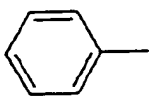
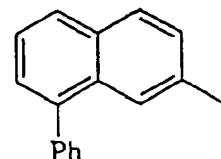
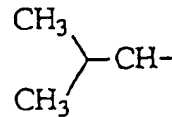
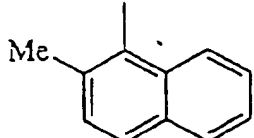
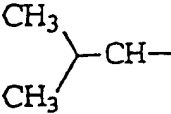
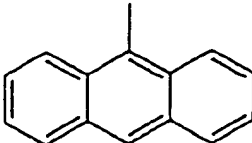
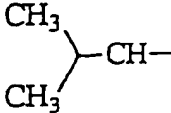
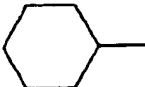
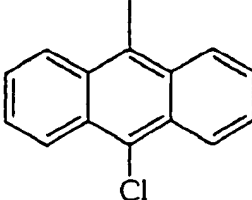
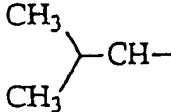
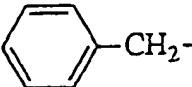
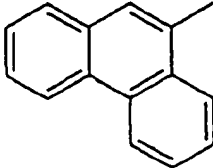
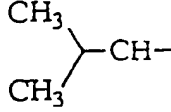
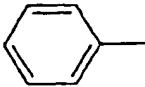
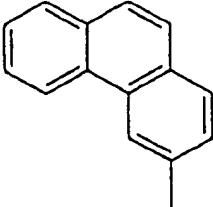
R^1	R^2	Ar
	CH_3	
	<i>t</i> -Bu	
		
		
		
	CH_3	

Table 1 (continued)

R^1	R^2	Ar
	t-Bu	
		
		
		

- 18 -

Table 1 (continued)

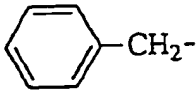
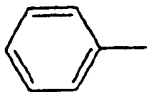
R^1	R^2	Ar
	CH_3	
	<i>t</i> -Bu	
		
		
	CH_3	

Table 1 (continued)

R^1	R^2	Ar
	t-Bu	

Table 1 (continued)

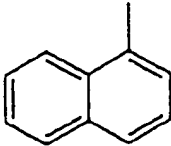
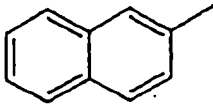
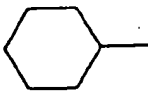
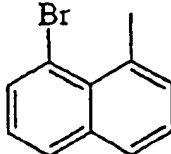
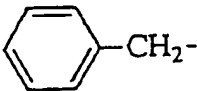
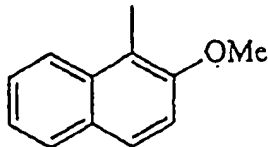
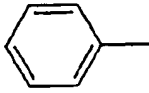
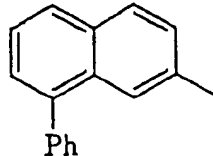
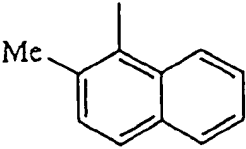
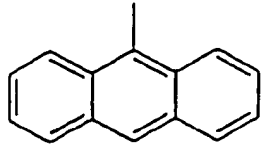
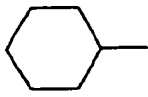
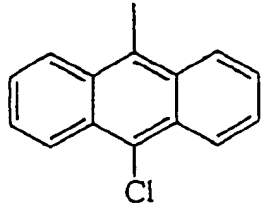
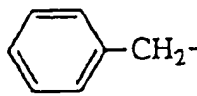
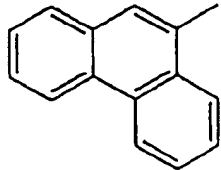
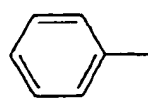
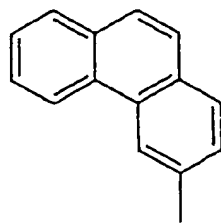
R^1	R^2	Ar
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$	CH_3	
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$	t-Bu	
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$		
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$		
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$		
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$	CH_3	

Table 1 (continued)

R^1	R^2	Ar
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$	<i>t</i> -Bu	
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$		
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$		
$\text{CH}_3\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}\text{CH}_2-$		

- 22 -

Table 1 (continued)

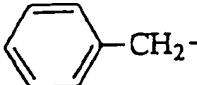
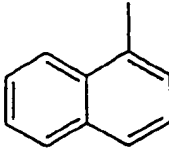
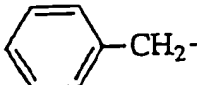
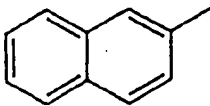
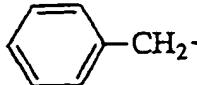
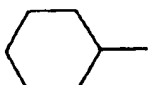
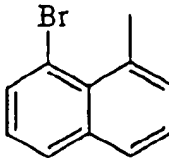
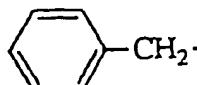
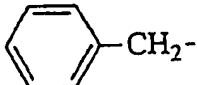
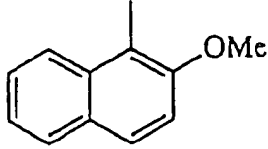
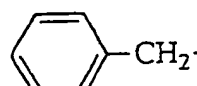
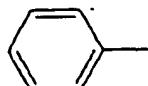
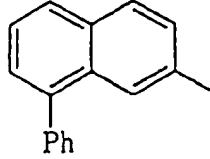
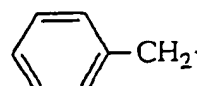
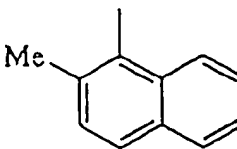
R^1	R^2	Ar
	CH_3	
	t-Bu	
		
		
		
	CH_3	

Table 1 (continued)

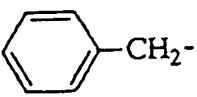
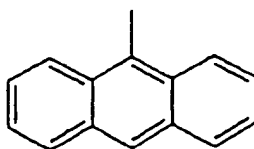
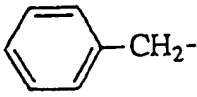
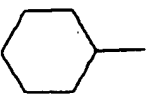
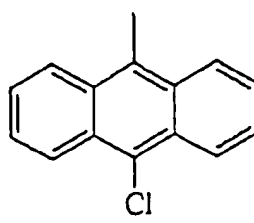
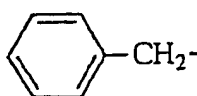
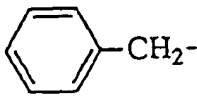
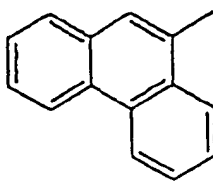
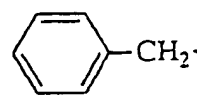
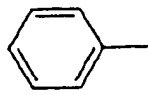
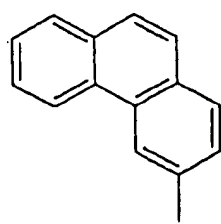
R^1	R^2	Ar
	t-Bu	
		
		
		

Table 1 (continued)

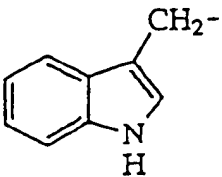
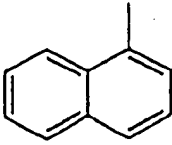
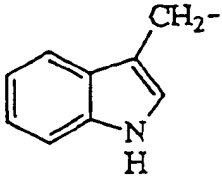
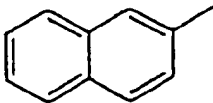
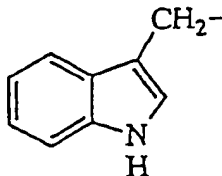
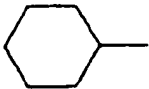
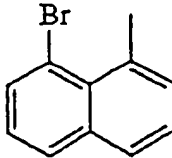
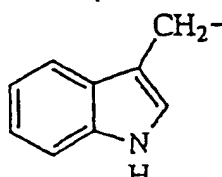
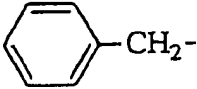
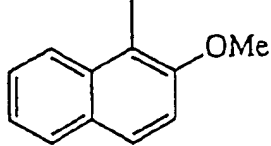
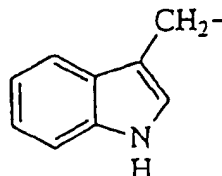
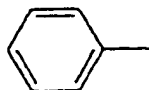
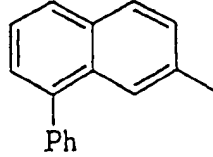
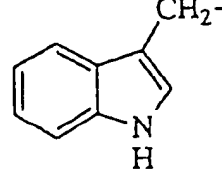
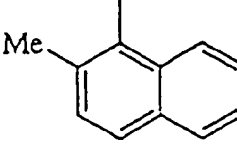
R ¹	R ²	Ar
	CH ₃	
	t-Bu	
		
		
		
	CH ₃	

Table 1 (continued)

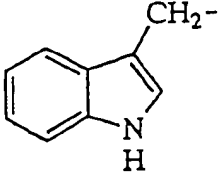
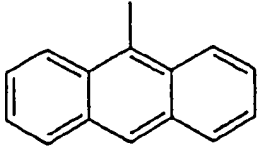
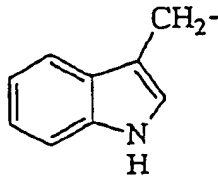
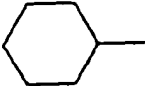
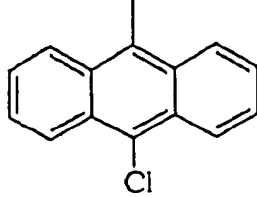
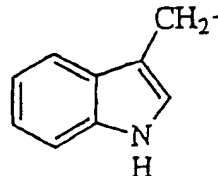
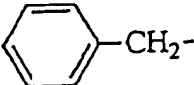
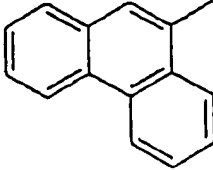
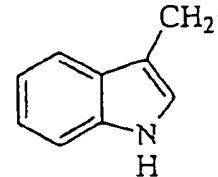
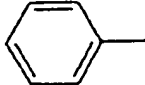
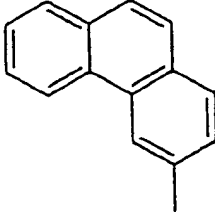
R^1	R^2	Ar
	t-Bu	
		
		
		

Table 1 (continued)

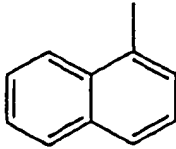
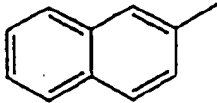
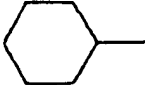
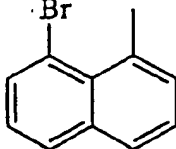
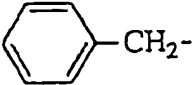
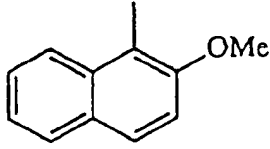
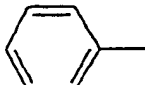
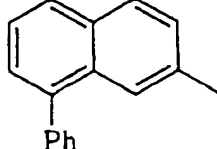
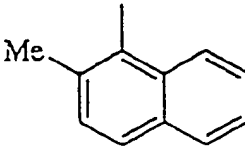
R^1	R^2	Ar
$CH_3S-CH_2CH_2-$	CH_3	
$CH_3S-CH_2CH_2-$	t-Bu	
$CH_3S-CH_2CH_2-$		
$CH_3S-CH_2CH_2-$		
$CH_3S-CH_2CH_2-$		
$CH_3S-CH_2CH_2-$	CH_3	

Table 1 (continued)

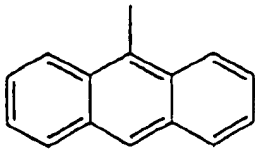
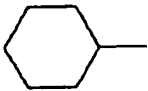
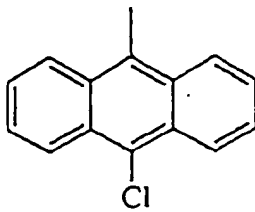
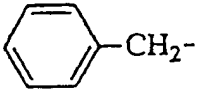
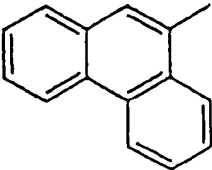
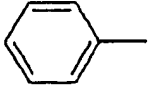
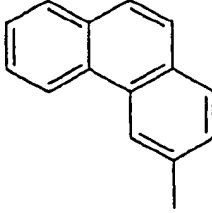
R^1	R^2	Ar
$CH_3S-CH_2CH_2-$	t-Bu	
$CH_3S-CH_2CH_2-$		
$CH_3S-CH_2CH_2-$		
$CH_3S-CH_2CH_2-$		

Table 1 (continued)

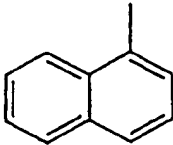
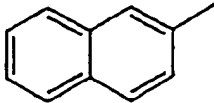
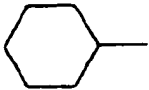
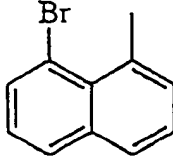
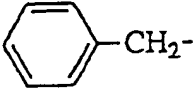
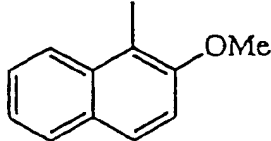
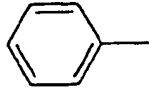
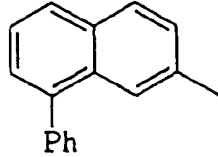
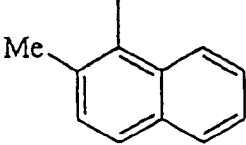
R^1	R^2	Ar
HO-CH ₂ -	CH ₃	
HO-CH ₂ -	t-Bu	
HO-CH ₂ -		
HO-CH ₂ -		
HO-CH ₂ -		
HO-CH ₂ -	CH ₃	

Table 1 (continued)

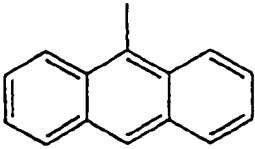
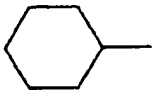
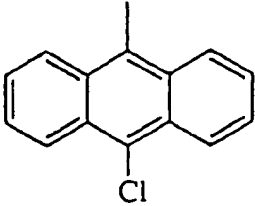
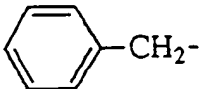
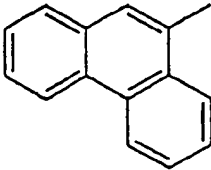
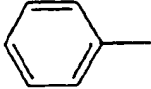
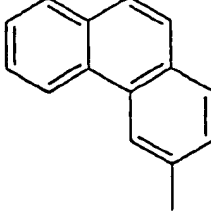
R^1	R^2	Ar
$\text{HO}\cdot\text{CH}_2\text{-}$	t-Bu	
$\text{HO}\cdot\text{CH}_2\text{-}$		
$\text{HO}\cdot\text{CH}_2\text{-}$		
$\text{HO}\cdot\text{CH}_2\text{-}$		

Table 1 (continued)

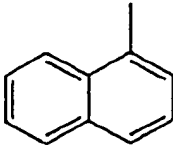
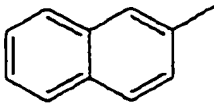
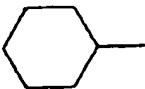
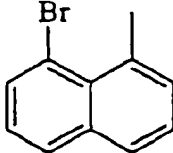
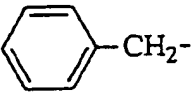
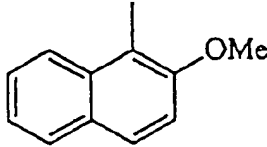
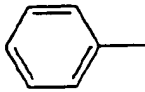
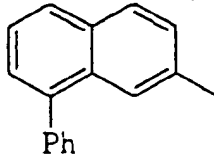
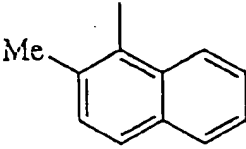
R^1	R^2	Ar
$\text{CH}_3\text{-}\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	CH_3	
$\text{CH}_3\text{-}\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	t-Bu	
$\text{CH}_3\text{-}\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$		
$\text{CH}_3\text{-}\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$		
$\text{CH}_3\text{-}\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$		
$\text{CH}_3\text{-}\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	CH_3	

Table 1 (continued)

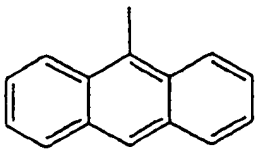
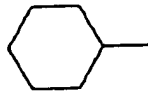
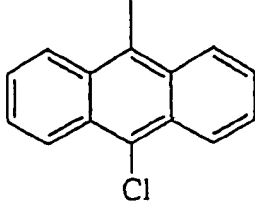
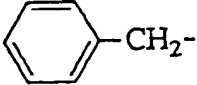
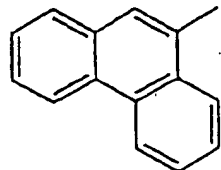
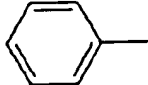
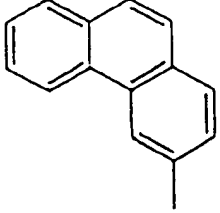
R^1	R^2	Ar
$\text{CH}_3\text{-CH-}$ $\quad\quad\text{OH}$	<i>t</i> -Bu	
$\text{CH}_3\text{-CH-}$ $\quad\quad\text{OH}$		
$\text{CH}_3\text{-CH-}$ $\quad\quad\text{OH}$		
$\text{CH}_3\text{-CH-}$ $\quad\quad\text{OH}$		

Table 1 (continued)

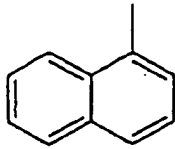
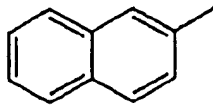
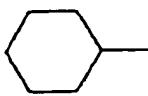
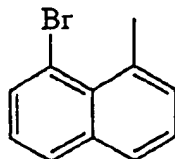
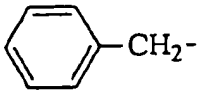
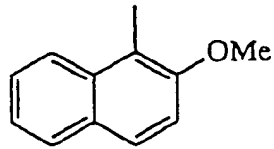
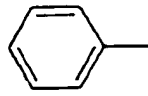
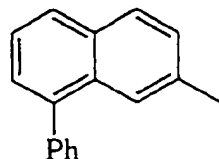
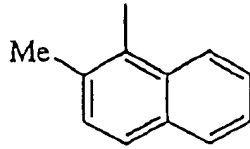
R^1	R^2	Ar
HS-CH ₂ -	CH ₃	
HS-CH ₂ -	t-Bu	
HS-CH ₂ -		
HS-CH ₂ -		
HS-CH ₂ -		
HS-CH ₂ -	CH ₃	

Table 1 (continued)

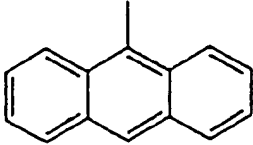
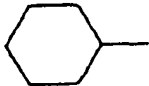
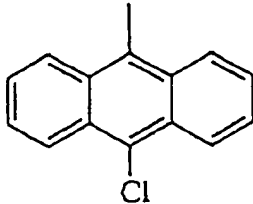
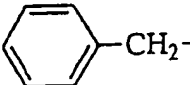
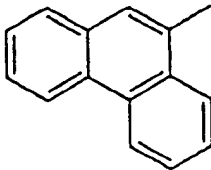
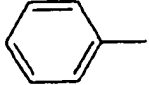
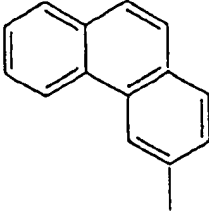
R^1	R^2	Ar
HS-CH ₂ -	t-Bu	
HS-CH ₂ -		
HS-CH ₂ -		
HS-CH ₂ -		

Table 1 (continued)

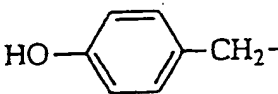
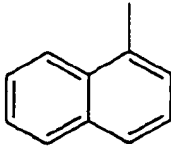
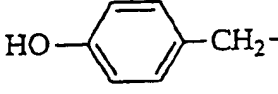
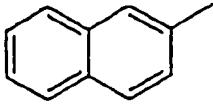

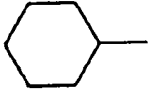
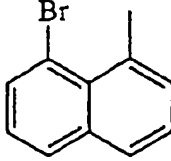

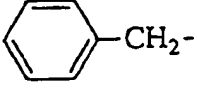
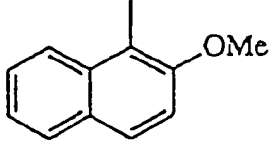

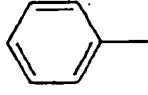
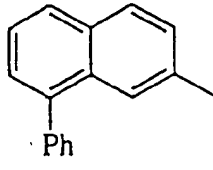

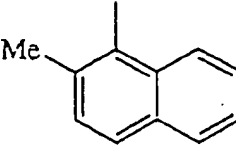
R^1	R^2	Ar
	CH_3	
	<i>t</i> -Bu	
		
		
		
	CH_3	

Table 1 (continued)


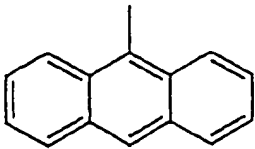

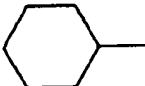
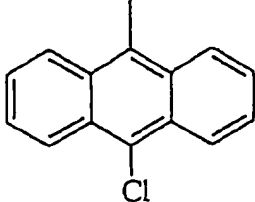

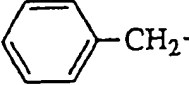
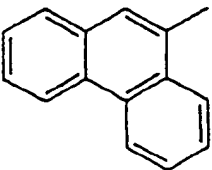

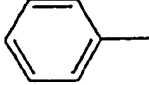
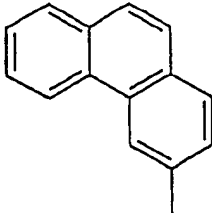
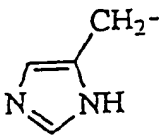
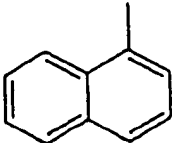
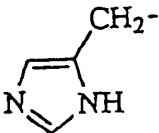
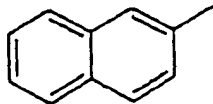
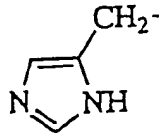
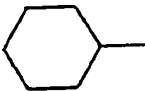
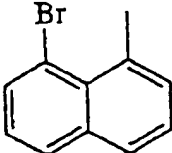
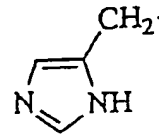
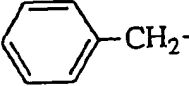
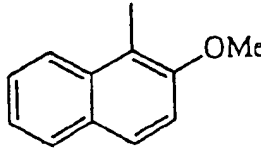
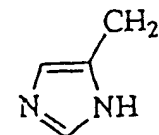
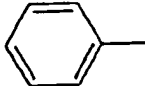
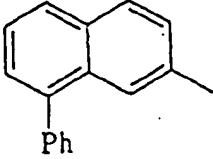
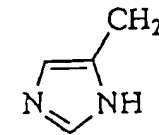
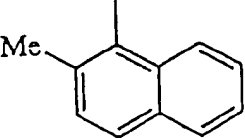
R^1	R^2	Ar
	t-Bu	
		
		
		

Table 1 (continued)

R ¹	R ²	Ar
	CH ₃	
	t-Bu	
		
		
		
	CH ₃	

- 37 -

Table 1 (continued)

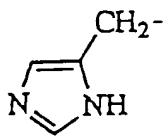
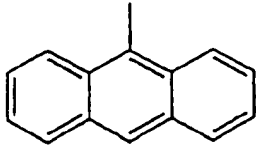
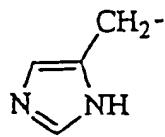
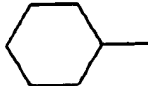
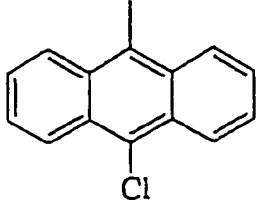
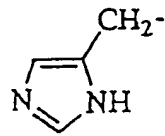
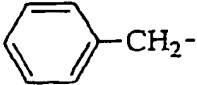
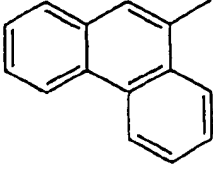
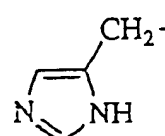
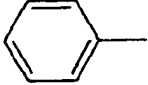
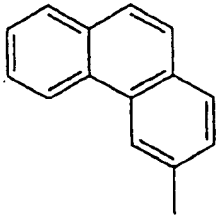
R^1	R^2	Ar
	t-Bu	
		
		
		

Table 1 (continued)

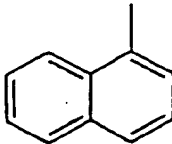
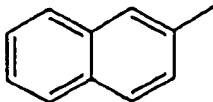
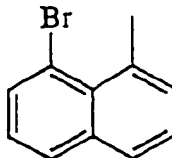
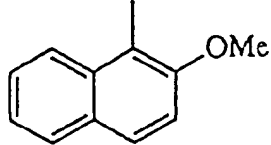
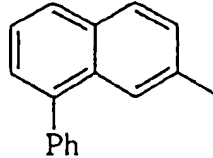
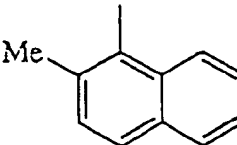
R^1	R^2	Ar
$-(CH_2)_3-$		
$-(CH_2)_3-$		
$-(CH_2)_3-$		
$-(CH_2)_3-$		
$-(CH_2)_3-$		
$-(CH_2)_3-$		

Table 1 (continued)

R^1	R^2	Ar
$-(CH_2)_3-$		
$-(CH_2)_3-$		
$-(CH_2)_3-$		
$-(CH_2)_3-$		

Table 1 (continued)

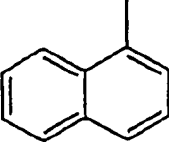
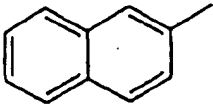
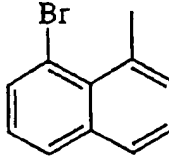
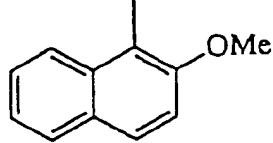
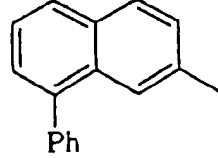
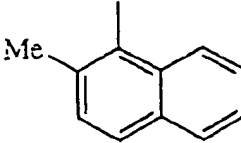
R^1	R^2	Ar
$-(CH_2)_4-$		
$-(CH_2)_4-$		
$-(CH_2)_4-$		
$-(CH_2)_4-$		
$-(CH_2)_4-$		
$-(CH_2)_4-$		

Table 1 (continued)

R^1	R^2	Ar
$-(CH_2)_4-$		
$-(CH_2)_4-$		
$-(CH_2)_4-$		
$-(CH_2)_4-$		

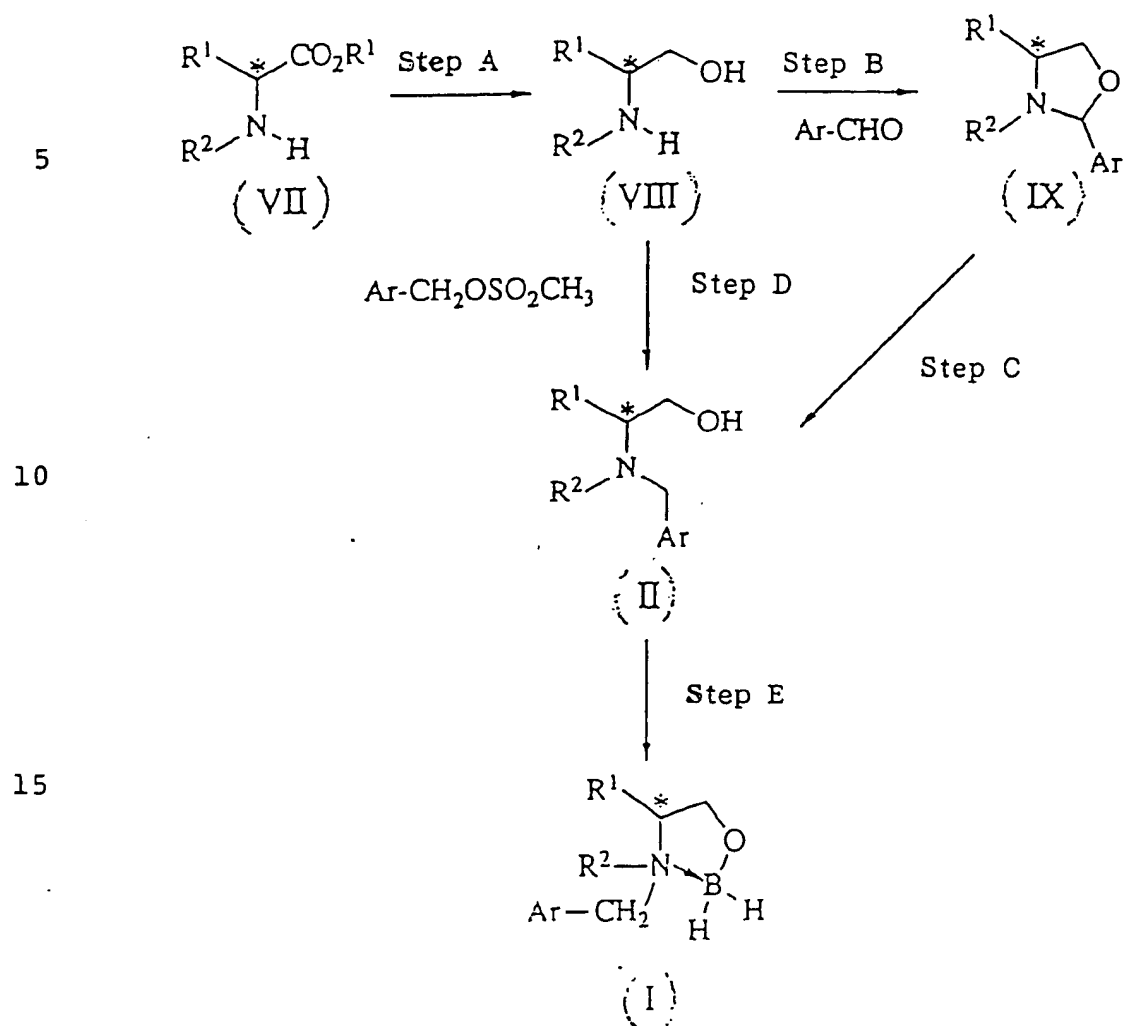
- 42 -

Now, the synthesis of the borane complex (I) and the asymmetric reaction of a carbonyl compound using the borane complex will be described in detail.

The optically active β -aminoalcohol compound (II) and
5 its borane complex (I) according to the present invention, can readily be produced in good yield in two or three steps using, as starting material, an optically active β -aminoalcohol (VIII) which is again readily available from an amino acid ester, by known methods
10 (JIKKEN KAGAKU KOZA 17, YUKI KAGOBUTSU NO HANNO (GE) p. 25, P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, 31, 1617 (1948); P. Karrer and P. Portmann, *ibid.*, 32, 1034 (1949); P. Karrer, P. Portmann and M. Suter, *ibid.*, 32, 1156 (1949); R. R. Gebhard and P. Karrer, *ibid.*, 38, 915 (1955); *Synthetic Methods of Organic Chemistry* Vol. 11, 52; H. Bauer, E. Adams and H. Tabor, *Biochem. Prep.* 4, 46 (1955)).

The following reaction scheme represents a synthetic route of the optically active β -aminoalkoxyborane complex
20 of the formula (I) and the optically active β -aminoalcohol compound of the formula (II). In the formulas, R^1 , R^2 and Ar are as defined above.

- 43 -



Step A is a reduction reaction of the ester moiety of the amino acid ester (VII) to an alcohol (VIII). As the reducing agent, lithium aluminum hydride, diisobutylaluminum hydride, sodium dialkoxyaluminum hydride or lithium borohydride may, for example, be used. Preferably, lithium aluminum hydride is employed. As the solvent for reaction, an ether type solvent such as

- 44 -

diethyl ether, di-n-propyl ether, tetrahydrofuran, 1,3-
or 1,4-dioxane may be employed. Preferably, diethyl
ether or tetrahydrofuran is employed. The reaction can
be conducted within a temperature range of from -78°C to
5 60°C, preferably from -10°C to 20°C.

Step B is a reaction for forming an oxazolidine ring
by a dehydration condensation reaction of the β -
aminoalcohol (VIII) obtained in Step A with the aromatic
aldehyde. The solvent for reaction may, for example, be
10 an alcohol solvent such as methanol, ethanol, n-propanol
or i-propanol, a polar solvent such as acetonitrile,
dimethylformamide or dimethylsulfoxide, a halogen-type
solvent such as dichloromethane, 1,1- or 1,2-
dichloroethane, chloroform or carbon tetrachloride, or an
15 ether type solvent such as diethyl ether, di-n-propyl
ether, tetrahydrofuran, 1,3- or 1,4-dioxane. Preferably,
methanol, acetonitrile or tetrahydrofuran is employed.
The reaction can be conducted within a temperature range
of from -78°C to 60°C, preferably from -10°C to 30°C.

20 Step C is a reaction to obtain an N-(aryl)methyl- β -
aminoalcohol compound (II) by reductive ring-opening of
the oxazolidine compound (IX) obtained in step B. As the
reducing agent, lithium aluminum hydride, diisobutyl
aluminum hydride, sodium dialkoxyaluminum hydride,
25 lithium borohydride, potassium borohydride or sodium
borohydride may, for example, be employed. Preferably,
potassium, borohydride or sodium borohydride is employed.

- 45 -

The solvent for reaction may, for example, be an alcohol-type solvent such as methanol, ethanol, n-propanol or i-propanol, or an ether-type solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, 1,3- or 1,4-dioxane.

5 Preferably, methanol, ethanol or tetrahydrofuran is employed. The reaction can be conducted within a temperature range of from -78°C to 60°C, preferably from -10°C to 20°C.

Step D is another synthetic route for the N-

10 (aryl)methyl- β -aminoalcohol compound (II). Namely, the N-(aryl)methyl- β -aminoalcohol compound (II) is obtained by the reaction of the β -aminoalcohol compound (VIII) with the corresponding arylmethyl ester of sulfonic acid.

As the sulfonate having an arylmethyl group,

15 methylate, benzene sulfonate, p-chlorobenzene sulfonate, p-toluene sulfonate, p-nitrobenzene sulfonate or trifluoromethane sulfonate may, for example, be employed. Preferably methylate is employed. As the base, a tertiary or unsaturated amine such as triethylamine,

20 trimethylamine, pyridine, DBU (1,8-diazabicyclo[5.4.0]-7-undecene) or DBN (1,5-diazabicyclo[4.3.0]-5-nonene) may be employed. Preferably triethylamine is employed. The solvent for reaction may, for example, be an ether-type solvent such as diethyl ether, di-n-propyl ether,

25 tetrahydrofuran, 1,3- or 1,4-dioxane, a polar solvent such as acetonitrile, dimethylformamide or dimethylsulfoxide, or a halogen-type solvent such as

- 46 -

dichloromethane, 1,1- or 1,2-dichloroethane, chloroform, or carbon tetrachloride. Preferably dichloromethane or chloroform is employed, more preferably dichloromethane is employed. The reaction can be conducted within a
5 temperature range of from -78°C to 60°C, preferably from -10°C to 30°C.

Step E is a reaction for synthesizing the β -aminoalkoxyborane complex (I) by the reaction of the N-(aryl)methyl- β -aminoalcohol compound (II) obtained in
10 Step C or D with a borane reagent. As the borane reagent, a borane-tetrahydrofuran complex, a borane-diethyl ether complex, a borane-pyridine complex, a borane-ammonia complex, a borane-tert-butylamine complex, a borane-N,N-diethylaniline complex, a
15 borane-N,N-diisopropylethylamine complex, a borane-dimethylamine complex, a borane-4-dimethylaminopyridine complex, a borane-4-ethylmorpholine complex, a borane-methylsulfide complex, a borane-trimethylamine complex, a
20 borane-triphenylphosphine complex or a borane-triphenylphosphite complex, may, for example, be used. Preferably, a borane-tetrahydrofuran complex or a borane-diethyl ether complex is used. More preferably, a borane-tetrahydrofuran complex is employed. The solvent
25 for reaction may, for example, be an alcohol such as methanol, ethanol, n-propanol or i-propanol, a polar solvent such as acetonitrile, dimethylformamide or

- 47 -

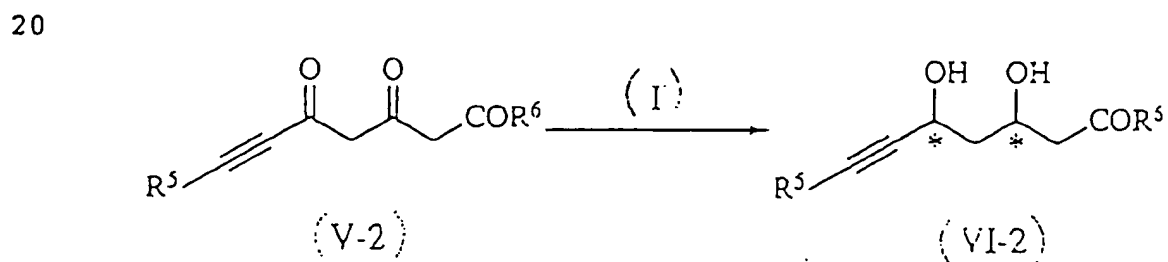
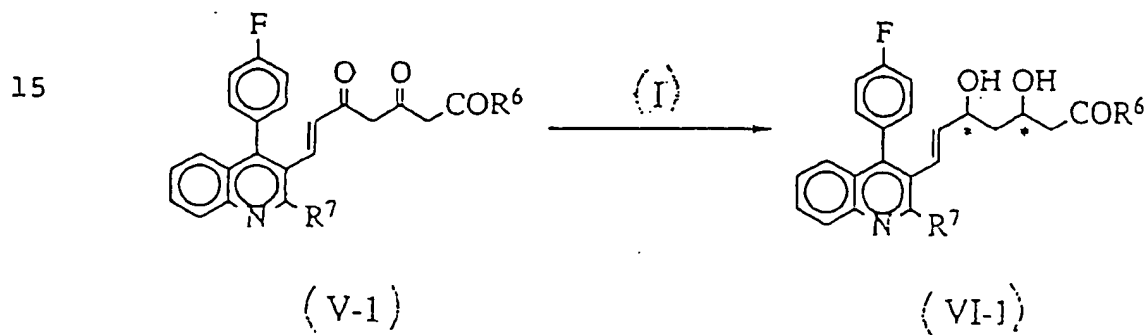
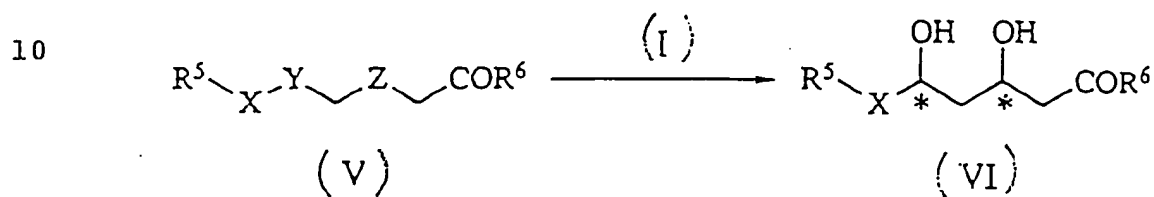
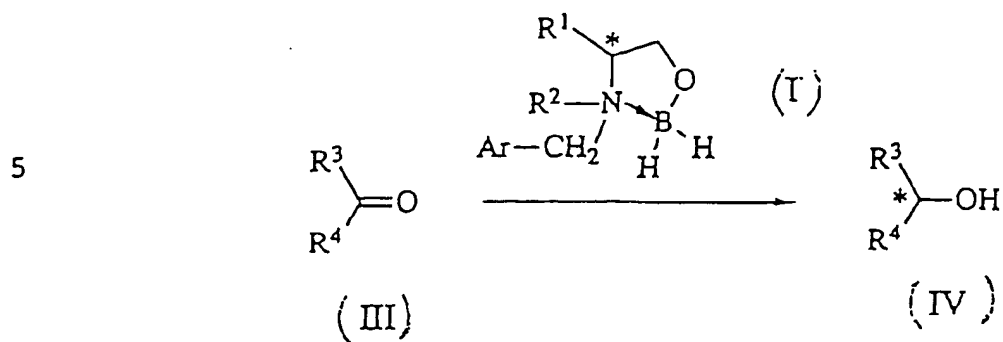
dimethylsulfoxide, a halogen-type solvent such as dichloromethane, 1,1- or 1,2-dichloroethane, chloroform or carbon tetrachloride, or an ether-type solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, 1,3-
5 or 1,4-dioxane. Preferably, methanol, dichloromethane, diethyl ether or tetrahydrofuran is used. More preferably, tetrahydrofuran is used. The reaction can be conducted within a temperature range of from -100°C to 80°, preferably from -78°C to 40°C.

10 The β -aminoalkoxyborane complex (I) is stable against light, water and heat and soluble in various solvents, and thus has a merit that it is very easy to handle for experiments.

Further, in some cases, the β -aminoalkoxyborane
15 complex (I) may be formed in the reaction system by adding the N-(aryl)methyl- β -aminoalcohol compound (II) and the borane reagent to the reaction system at the time of the reduction reaction of the carbonyl compound, without separating it for use.

20 The carbonyl compound (III) or (V) is stereoselectively reduced by means of the optically active β -aminoalkoxyborane complex (I) obtained in Step E to obtain the corresponding optically active alcohol compound (IV) or (VI).

- 48 -



25

The respective substituents of the compounds of the formulas (III), (IV), (V) and (VI) will now be described.

- 49 -

R^3 and R^4 differ from each other and represent C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkenyl, C_7 - C_{11} aralkyl or C_6 - C_{14} aryl. Otherwise, R^3 and R^4 may together form a cyclic

5 structure.

C_1 - C_{10} alkyl includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decanyl.

10 C_3 - C_{10} cycloalkyl includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecanyl.

C_2 - C_{10} alkenyl includes, for example, vinyl, 1-propenyl, 1-methylethenyl, 2-propenyl, 1,2-dimethyl-1-propenyl, 1-butenyl, 1-pentenyl, 1-hexenyl, 1-heptenyl, 15 1-octenyl, 1-nonenyl and 1-decenyl.

C_2 - C_{10} alkynyl includes, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 3-methyl-1-butyne, 1-pentyne, 1-hexynyl, 1-heptynyl, 1-octynyl, 1-nonyl and 20 1-decynyl.

C_3 - C_{10} cycloalkenyl includes, for example, 2-cyclopropenyl, 1-cyclobutenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl and 3-cyclohexenyl.

C_7 - C_{11} aralkyl is the same as the corresponding 25 substituent for R^1 .

C_6 - C_{14} aryl includes, for example, phenyl, o-tolyl, m-tolyl, p-tolyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl,

- 50 -

2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-
 dimethylphenyl, 3,5-dimethylphenyl, 2,3,4-
 trimethylphenyl, 3,4,6-trimethylphenyl, 2,4,6-
 trimethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-
 5 chlorophenyl, 3,4-dichlorophenyl, 2-methoxyphenyl, 3-
 methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-
 nitrophenyl, α -naphthyl, β -naphthyl, (2-methyl)-2-
 naphthyl, (3-methyl)-1-naphthyl, (4-methyl)-1-naphthyl,
 (5-methyl)-1-naphthyl, (6-methyl)-1-naphthyl, (7-methyl)-
 10 1-naphthyl, (8-methyl)-1-naphthyl, (1-methyl)-2-naphthyl,
 (3-methyl)-2-naphthyl, (4-methyl)-2-naphthyl, (5-methyl)-
 2-naphthyl, (6-methyl)-2-naphthyl, (7-methyl)-2-naphthyl,
 (8-methyl)-2-naphthyl, (2-ethyl)-1-naphthyl, (3-ethyl)-1-
 naphthyl, (4-ethyl)-1-naphthyl, (5-ethyl)-1-naphthyl,
 15 (6-ethyl)-1-naphthyl, (7-ethyl)-1-naphthyl, (8-ethyl)-1-
 naphthyl, (1-ethyl)-2-naphthyl, (3-ethyl)-2-naphthyl, (4-
 ethyl)-2-naphthyl, (5-ethyl)-2-naphthyl, (6-ethyl)-2-
 naphthyl, (7-ethyl)-2-naphthyl, (8-ethyl)-2-naphthyl, (2-
 propyl)-1-naphthyl, (3-propyl)-1-naphthyl, (4-propyl)-1-
 20 naphthyl, (5-propyl)-1-naphthyl, (6-propyl)-1-naphthyl,
 (7-propyl)-1-naphthyl, (8-propyl)-1-naphthyl, (1-propyl)-
 2-naphthyl, (3-propyl)-2-naphthyl, (4-propyl)-2-naphthyl,
 (5-propyl)-2-naphthyl, (6-propyl)-2-naphthyl, (7-propyl)-
 2-naphthyl, (8-propyl)-2-naphthyl, 1-anthryl, 2-anthryl,
 25 9-anthryl, 1-phenanthryl, 3-phenanthryl, 4-phenanthryl
 and 9-phenanthryl.

The cyclic structure formed by R³ and R⁴ together

- 51 -

includes, for example, 1-methylcyclobutanone, 2,2-dimethylcyclobutanone, 2,2-ethylcyclobutanone, 2,2-di-n-cyclobutanone, 2,2-di-i-propylcyclobutanone, 2,2-di-n-butylcyclobutanone, 2,2-di-i-butylcyclobutanone, 2,2-di-
 5 sec-butylcyclobutanone, 2,2-di-tert-butylcyclobutanone, 2,2-di-n-pentylcyclobutanone, 2,2-di-n-hexylcyclobutanone, 1-methylcyclopentanone, 2,2-dimethylcyclopentanone, 2,2-diethylcyclopentanone, 2,2-di-n-propylcyclopentanone, 2,2-di-i-propylcyclopentanone,
 10 2,2-di-n-butylcyclopentanone, 2,2-di-i-butylcyclopentanone, 2,2-di-sec-butylcyclopentanone, 2,2-di-tert-butylcyclopentanone, 2,2-di-n-pentylcyclopentanone, 2,2-di-n-hexylcyclopentanone, trimethylcyclohexanone, 2,2-dimethylcyclohexanone, 2,2-
 15 diethylcyclohexanone, 2,2-di-n-propylcyclohexanone, 2,2-di-i-propylcyclohexanone, 2,2-di-n-butylcyclohexanone, 2,2-di-i-butylcyclohexanone, 2,2-di-sec-butylcyclohexanone, 2,2-di-tert-butylcyclohexanone, 2,2-di-n-pentylcyclohexanone, 2,2-di-n-hexylcyclohexanone,
 20 cyclobutenone, 2-cyclopentenone, 2-cyclohexenone, 2-cycloindanone and 1-tetralone.

X represents a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-(\text{CH}_3)\text{C}=\text{CH}-$, $-\text{CH}=\text{C}(\text{CH}_3)-$ or $-\text{C}\equiv\text{C}-$.

When X is a bond, R^5 is CHO , $\text{CH}(\text{OR}^9)(\text{OR}^{10})$ (wherein
 25 each of R^9 and R^{10} which are independent of each other, is hydrogen or C_1 - C_3 alkyl, or R^9 and R^{10} together form C_2 - C_5 alkylene), $\text{CH}_2\text{OR}^{11}$ (wherein R^{11} is hydrogen, C_1 - C_3

- 52 -

alkyl, benzyl which may be substituted by methyl or methoxy, trityl, tetrahydropyranyl, methoxymethyl, trimethylsilyl, dimethyl-tert-butylysilyl or diphenyl-tert-butylysilyl), CH_2R^{12} (wherein R^{12} is fluoro, chloro, bromo or iodo), CN , CO_2R^{13} (wherein R^{13} is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, or benzyl which may be substituted by methyl or methoxy), or $\text{CONR}^{14}\text{R}^{15}$ (wherein each of R^{14} and R^{15} which are independent of each other, is hydrogen, $\text{C}_1\text{-C}_3$ alkyl group, benzyl, 1-methylbenzyl, or phenyl which may be substituted by methyl or methoxy).

Each of R^9 and R^{10} which are independent of each other, may be hydrogen, methyl, ethyl, n-propyl or i-propyl, or R^9 and R^{10} may together form ethylene, trimethylene or 2,2-dimethyl-1,3-trimethylene.

R^{11} may be hydrogen, methyl, ethyl, n-propyl, i-propyl, o-methylbenzyl, m-methylbenzyl, p-methylbenzyl, o-methoxybenzyl, m-methoxybenzyl, p-methoxybenzyl, trithyl, tetrahydropyranyl, methoxymethyl, trimethylsilyl, dimethyl-tert-butylysilyl or diphenyl-tert-butylysilyl.

R^{12} is fluoro, chloro, bromo or iodo.

R^{13} may be hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, o-methylbenzyl, m-methylbenzyl, p-methylbenzyl, o-methoxybenzyl, m-methoxybenzyl or p-methoxybenzyl.

Each of R^{14} and R^{15} which are independent of each other, may be hydrogen, methyl, ethyl, n-propyl, i-

- 53 -

propyl, benzyl, 1-methylbenzyl, o-methylphenyl, o-methylphenyl, p-methylphenyl, o-methoxyphenyl, m-methoxyphenyl or p-methoxyphenyl.

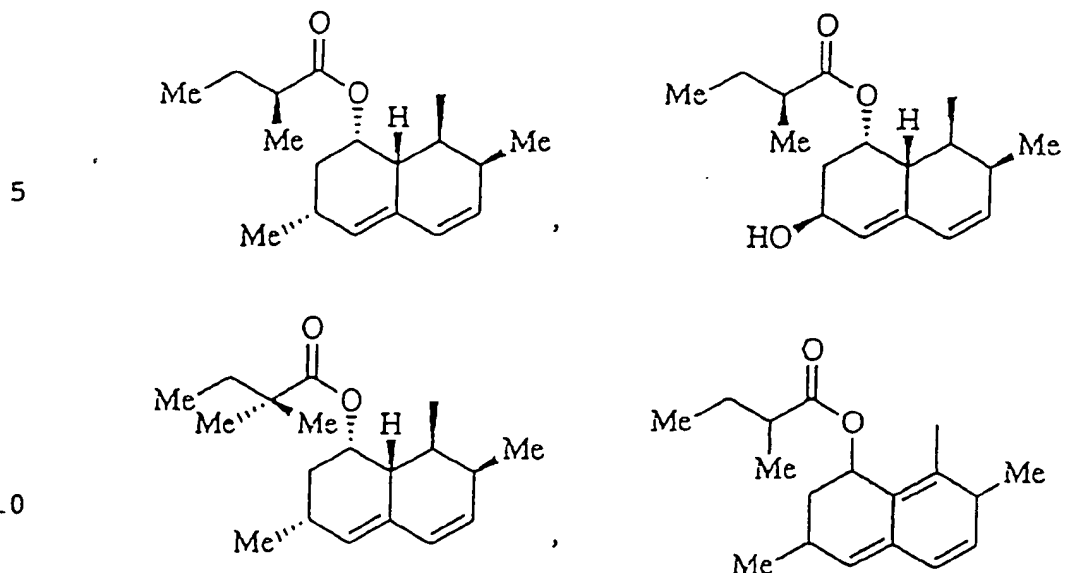
When X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-(\text{CH}_3)\text{C}=\text{CH}-$,
5 $-\text{CH}=\text{C}(\text{CH}_3)-$ or $-\text{C}\equiv\text{C}-$, R^5 is hydrogen, trialkylsilyl, a carbon ring aliphatic group, a carbon ring aromatic group, a heterocyclic aromatic group, a condensed heterocyclic aromatic group, a chain unsaturated aliphatic group or a cyclic unsaturated aliphatic group.
10 cyclic unsaturated aliphatic group.

Trialkylsilyl includes, for example, trimethylsilyl, triethylsilyl, tri-n-propylsilyl, tri-i-propylsilyl, tri-n-butylsilyl, tri-i-butylsilyl, tri-n-hexylsilyl, dimethylethylsilyl, dimethyl-n-propylsilyl, dimethyl-n-
15 butylsilyl, dimethyl-i-butylsilyl, dimethyl-tert-butylsilyl, dimethyl-n-pentylsilyl, dimethyl-n-octylsilyl, dimethylcyclohexylsilyl, dimethylhexylsilyl, dimethyl-2,3-dimethylpropylsilyl, dimethyl-2-(bicycloheptyl)silyl, dimethylbenzylsilyl,
20 dimethylphenylsilyl, dimethyl-p-tolylsilyl, dimethylfropemecylsilyl, methyldiphenylsilyl, triphenylsilyl, diphenyl-tert-butylsilyl, tribenzylsilyl, diphenylvinylsilyl, diphenyl-n-butylsilyl and phenylmethylvinylsilyl.

25 The carbon ring aliphatic group may, for example, be hexahydronaphthyl or tetrahydronaphthyl, which may be substituted by one or more members selected from R^7 , C_2-

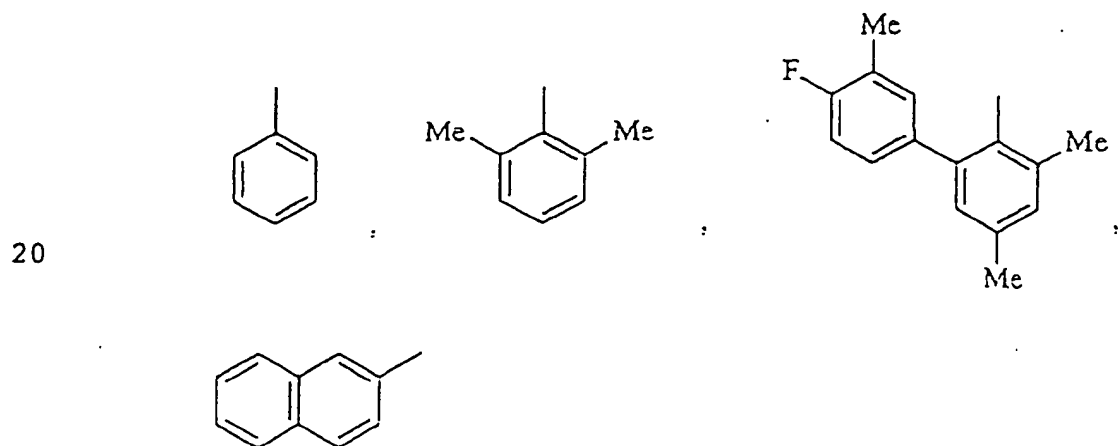
- 54 -

C₆ acyloxy and hydroxy, preferably the following:



The carbon ring aromatic group may, for example, be phenyl or naphthyl, which may be substituted by from 1 to 3 members selected from R⁷ and/or 1 or 2 substituents selected from R⁸, preferably the following:

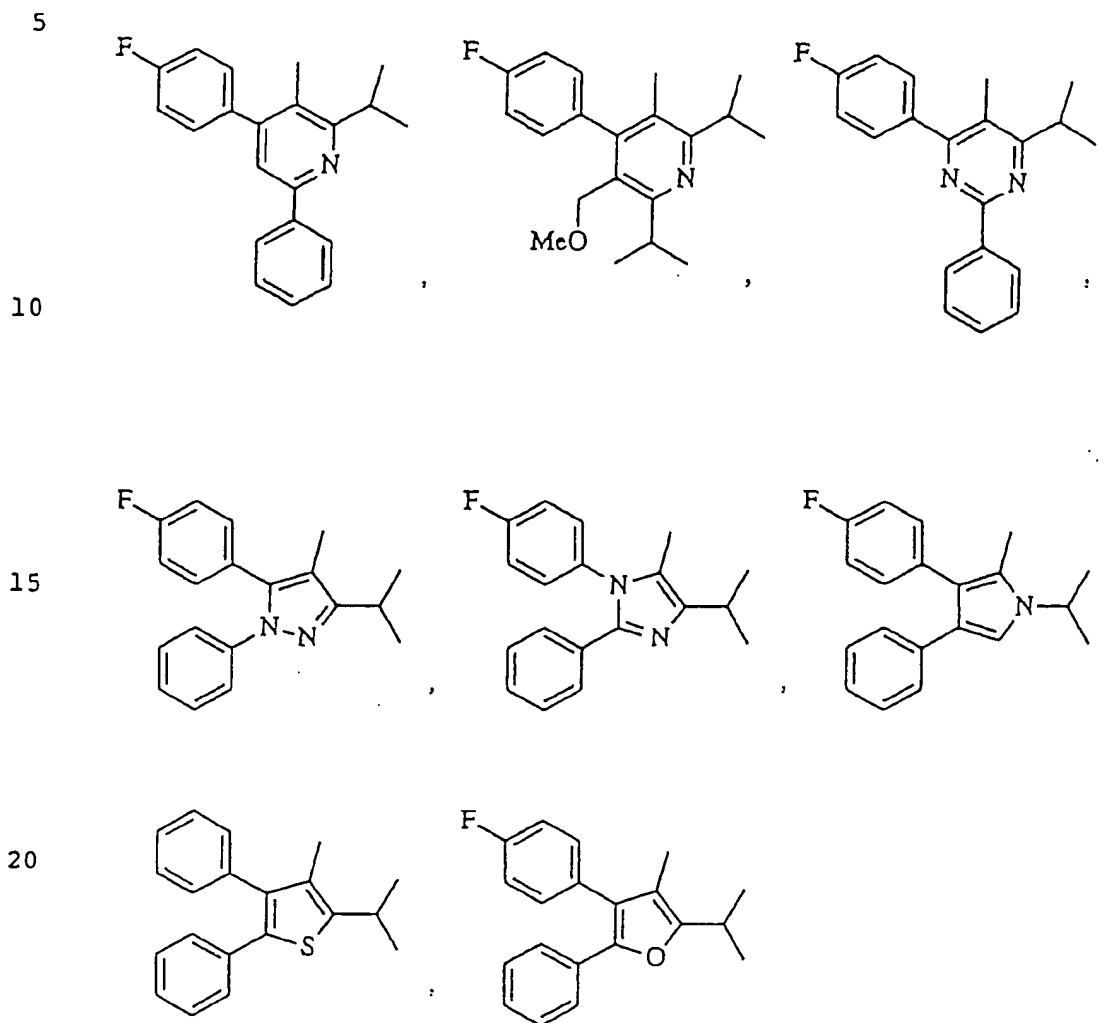
15



The heterocyclic aromatic group may, for example, be pyridyl, pyrimidinyl, pyrazolyl, imidazolyl, pyrrolyl, thienyl or furanyl, which may be substituted by from 1 to

- 55 -

3 members selected from R^7 , C_1-C_3 alkoxymethyl, phenylcarbamoyl and/or 1 or 2 substituents selected from R^8 , preferably the following:

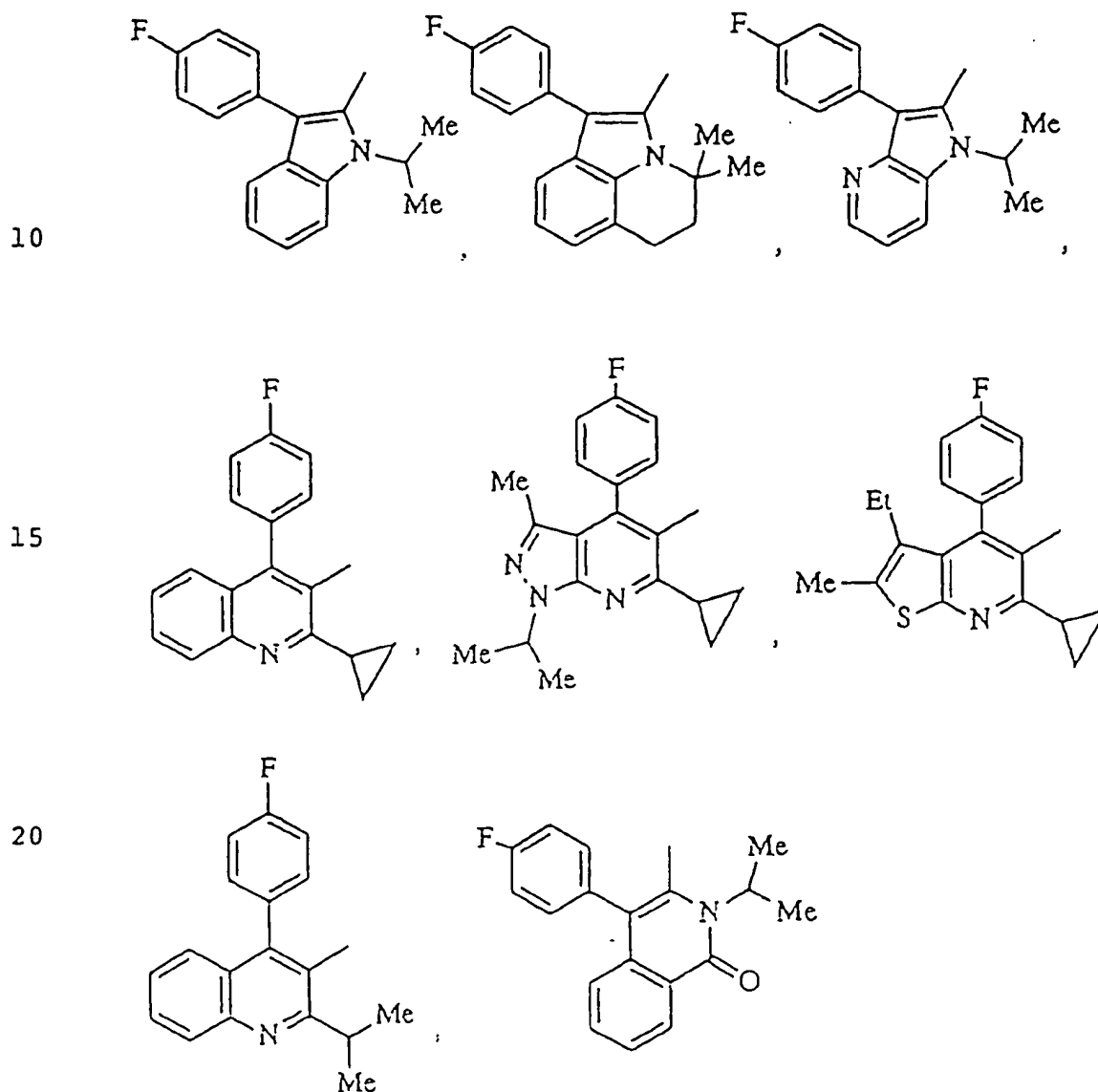


The condensed heterocyclic aromatic group may, for example, be indolyl, quinolyl, pyrazolopyridyl,

- 56 -

thienopyridyl, pyrrolopyridyl or isoquinolinonyl, which may be substituted by from 1 to 3 members selected from R^7 , C_1 - C_3 alkoxymethyl, phenylcarbamoyl and/or 1 or 2 substituents selected from R^8 , preferably the following:

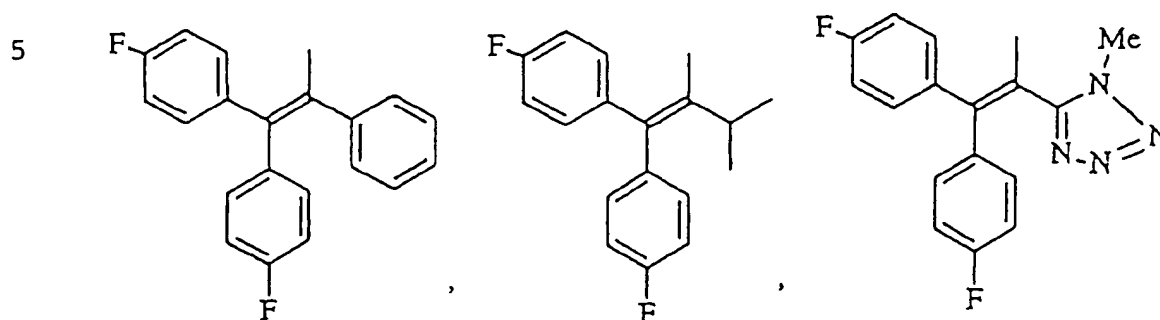
5



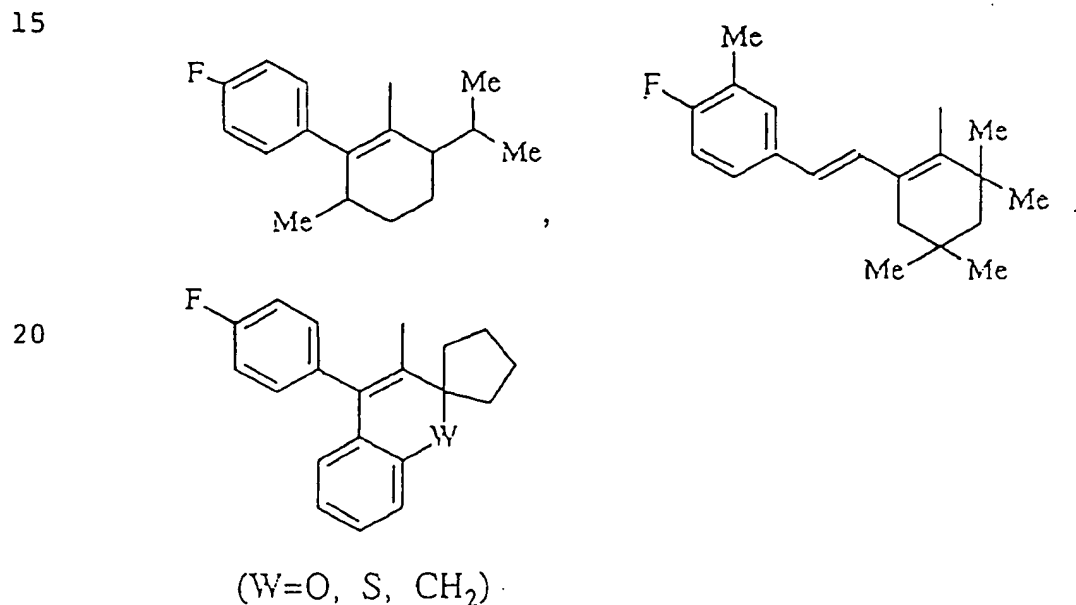
The chain unsaturated aliphatic group may, for example, be ethenyl or ethynyl, which may be substituted

- 57 -

by one member selected from R^7 , one or two members selected from R^8 and/or tetrazolyl, preferably the following:



The cyclic unsaturated aliphatic group may, for example, be cyclohexenyl which may be substituted by from 1 to 4 members selected from R^7 and/or 1 or 2 substituents selected from R^8 , preferably the following:



Y and Z which are independent of each other, is -CO- or -CH(OH)-, provided that the two are not simultaneously

- 58 -

-CH(OH)-.

R⁶ is hydroxyl, C₁-C₁₀ alkoxy, a metal oxy group or a C₀-C₇ amino group.

C₁-C₁₀ alkoxy includes, for example, methoxy, ethoxy,
5 n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy,
tert-butoxy, n-pentoxy, n-hexyloxy, n-heptyloxy, n-
octyloxy, n-nonyloxy, n-decanyloxy, cyclopropyloxy,
cyclobutyloxy, cyclopentyloxy, cyclohexyloxy,
cycloheptyloxy, cyclooctyloxy, cyclononyloxy,
10 cyclodecanyloxy, 2-propenyloxy, cis-2-butenyloxy, trans-
2-butenyloxy, β -methacryloxy, benzyloxy, o-
methylbenzyloxy, m-methylbenzyloxy, p-methylbenzyloxy,
phenoxy, o-methylphenoxy, m-methylphenoxy, p-
methylphenoxy, 2,3-dimethylphenoxy, 2,4-dimethylphenoxy,
15 2,5-dimethylphenoxy, 2,6-dimethylphenoxy, 3,4-
dimethylphenoxy, 3,5-dimethylphenoxy, α -naphthyloxy and
 β -naphthyloxy.

OM represents a carboxylate group, and M represents
lithium, sodium, potassium, calcium or NHR'₃ (wherein R'
20 is hydrogen, C₁-C₃ alkyl, C₃-C₇ cycloalkyl, C₂-C₅ alkenyl,
phenyl or benzyl), preferably sodium, potassium,
ammonium, trimethyl ammonium, triethyl ammonium, tri-n-
propyl ammonium, tribenzyl ammonium, triphenyl ammonium,
tricyclohexyl ammonium or trivinyl ammonium.

25 The C₀-C₇ amino group includes, for example, amino,
methylamino, ethylamino, dimethylamino, n-propylamino, i-
propylamino, methylamino, n-butylamino, i-butylamino,

- 59 -

sec-butylamino, tert-butylamino, methyl-n-propylamino,
methyl-i-propylamino, diethylamino, n-pentylamino,
methyl-n-butylamino, methyl-i-butylamino, methyl-sec-
butylamino, methyl-tert-butylamino, ethyl-n-propylamino,
5 ethyl-i-propylamino, n-hexylamino, methyl-n-pentylamino,
ethyl-n-butylamino, ethyl-i-butylamino, ethyl-sec-
butylamino, ethyl-tert-butylamino, di-n-propylamino, n-
propyl-i-propylamino, di-i-propylamino, cyclopropylamino,
cyclobutylamino, cyclopentylamino, cyclohexylamino,
10 dicyclohexylamino, N-methyl-N-phenylamino, α -
methylbenzylamino, 1-adiridiny, 1-azethinyl, 1-
pyrrolydiny, 1-piperidinyl and 1-pyrrolyl.

R^7 is C_1 - C_8 alkyl or C_3 - C_7 cycloalkyl. C_1 - C_8 alkyl
includes, for example, methyl, ethyl, n-propyl, i-propyl,
15 n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, n-
hexyl and n-heptyl. C_3 - C_7 cycloalkyl includes, for
example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl
and cycloheptyl.

R^8 is phenyl which may be substituted by C_1 - C_7 alkyl,
20 fluoro, chloro or bromo, and it may, for example, be
phenyl, 3-methylphenyl, 4-methylphenyl, 3,5-
dimethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3,5-
diethylphenyl, 3-methyl-5-ethylphenyl, 3-n-propylphenyl,
4-n-propylphenyl, 3,5-di-n-propylphenyl, 3-i-
25 propylphenyl, 4-i-propylphenyl, 3,5-di-i-propylphenyl, 3-
fluorophenyl, 4-fluorophenyl, 3,5-difluorophenyl, 3-
chlorophenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 3-

- 60 -

fluoro-4-chlorophenyl, 3-bromophenyl, 4-bromophenyl or 3,5-dibromophenyl.

The solvent for this reaction may, for example, be an alcohol-type solvent such as methanol, ethanol, n-
5 propanol or i-propanol, a polar solvent such as acetonitrile, dimethylformamide or dimethylsulfoxide, a halogen-type solvent such as dichloromethane, 1,1- or 1,2-dichloroethane, chloroform or carbon tetrachloride, or an ether-type solvent such as diethyl ether, di-n-
10 propyl ether, tetrahydrofuran, 1,3- or 1,4-dioxane. Preferably, methanol, dichloromethane, diethyl ether or tetrahydrofuran is employed. More preferably, tetrahydrofuran is employed. The reaction can be conducted within a temperature range of from -100°C to
15 80°C, preferably from -78°C to 40°C, more preferably from -10°C to 30°C.

To conduct this reaction stoichiometrically, the β -aminoalkoxyborane complex (I) is used in an amount of from 1 to 2 equivalent to the carbonyl compound (III) or
20 from 2 to 3 equivalent to the compound (V). On the other hand, to conduct this reaction catalytically, the β -aminoalcohol (II) is used in an amount of from 0.1 to 20 mol%, preferably from 1 to 10 mol%, and the borane reagent may, for example, be a borane-tetrahydrofuran
25 complex, a borane-diethyl ether complex, a borane-pyridine complex, a borane-ammonia complex, a borane-tert-butylamine complex, a borane-N,N-

- 61 -

diethylaniline complex, a borane·N,N-diisopropylethylamine complex, a borane·diethylamine complex, a borane·4-dimethylaminopyridine complex, a borane·4-ethylmorpholine complex, a borane·methylsulfide
5 complex, a borane·trimethylamine complex, a borane·triphenylphosphine complex or a borane·triphenylphosphite complex. Preferably, a borane·tetrahydrofuran complex or a borane·diethyl ether complex is employed. More preferably, a
10 borane·tetrahydrofuran complex is employed. Further, to facilitate the catalytic reaction, an alcohol-type solvent such as methanol, ethanol, n-propanol or i-propanol, preferably methanol or ethanol, more preferably methanol, is preferably used in an amount within a range
15 of from 3 to 10 equivalent, more preferably from 3 to 6 equivalent.

To improve the syn-selectivity in the asymmetric reduction reaction of a 1,3-dicarbonyl compound, a metal reagent such as a borane reagent, an aluminum reagent, a
20 silicon reagent, a tin reagent, a phosphorus reagent, a titanium reagent, a zinc reagent, a magnesium reagent or a calcium reagent, may be used.

The borane reagent may, for example, be an alkoxyborane reagent such as diethylmethoxyborane,
25 trimethoxyborane, tri-n-butoxyborane or catecholborane, a trialkylborane reagent such as triethylborane, triphenylborane, tri-n-butylborane, tri-sec-butylborane

- 62 -

or tri-tert-butylborane, or a dialkylborane reagent such as cyamelborane or bicyclo[3.3.1]nona-9-borane (9-BBN).

The aluminum reagent may, for example, be an aluminum trialkoxide reagent such as aluminum tri-i-propoxide, aluminum triethoxide, aluminum tri-n-butoxide or aluminum tri-sec-butoxide, or an alkylaluminum alkoxide reagent such as diethylaluminum ethoxide, di-n-propylaluminum ethoxide or di-i-propylaluminum ethoxide.

The silicon reagent may, for example, be a tetraalkoxysilane reagent such as tetramethoxysilane, tetraethoxysilane or tetraphenoxysilane, a trialkoxysilane reagent such as trimethoxy(methyl)silane, triethoxy(methyl)silane, trimethoxy(phenyl)silane, triethoxy(phenyl)silane, triethoxy(vinyl)silane or γ -chloropropyltrimethoxysilane, a dialkoxysilane reagent such as dimethoxydimethylsilane, diethoxydiethylsilane, dimethoxy(methyl)vinylsilane, diethoxy(methyl)silane, dimethoxy(ethyl)vinylsilane, diethoxy(methyl)vinylsilane, dimethoxydiphenylsilane or diethoxydiphenylsilane, a monoalkoxysilane reagent such as methoxytrimethylsilane, ethoxytrimethylsilane, methoxy(dimethyl)vinylsilane or ethoxy(dimethyl)vinylsilane, or a dihydroxysilane reagent such as dihydroxydimethylsilane, dihydroxydiethylsilane, dihydroxydi-n-propylsilane, dihydroxydi-i-propylsilane or dihydroxydiphenylsilane.

The tin reagent may, for example, be an alkyl(tin) acetate reagent such as tri-n-butyltin acetate, di-n-

- 63 -

butyltin diacetate or dioctyltin diacetate, or an alkyl(alkoxy)tin reagent such as dimethyldimethoxytin, diethyldimethoxytin, di-n-propyldimethoxytin, di-i-propyldimethoxytin, di-n-butyldimethoxytin, di-i-butyldimethoxytin, di-sec-butyldimethoxytin or di-tert-butyldimethoxytin.

The phosphorus reagent may, for example, be a triester of phosphorous acid such as trimethyl phosphite, triethyl phosphite, tri-i-propyl phosphite, tri-n-butyl phosphite or triphenyl phosphite.

The titanium reagent may, for example, be a titanium alkoxide such as tetraethyl orthotitanate, chlorotri-i-propyl orthotitanate, tetra-n-propyl orthotitanate, titanium tetra-i-propoxide or titanium tetra-n-butoxide.

The zinc reagent may, for example, be a zinc carboxylate such as zinc acetate, zinc propionate or zinc benzoate, a zinc halide such as zinc fluoride, zinc chloride, zinc bromide or zinc iodide, or an alkylzinc reagent such as dimethylzinc, diethylzinc, di-n-propylzinc or di-i-propylzinc.

The magnesium reagent may, for example, be a magnesium alkoxide reagent such as magnesium dimethoxide, magnesium diethoxide, magnesium di-n-propoxide or magnesium i-propoxide.

The calcium reagent may, for example, be a calcium alkoxide reagent such as calcium dimethoxide, calcium diethoxide, calcium di-n-propoxide or calcium i-

- 64 -

propoxide.

Among these metal reagents, preferred are diethylmethoxyborane, aluminum tri-*i*-propoxide and trichlorotri-*i*-propyl orthotitanate, and more preferred
5 are diethylmethoxyborane and aluminum tri-*i*-propoxide.

The metal reagent is used in an amount of from 1 to 3 equivalent, preferably from 1 to 1.2 equivalent, to the 1,3-dicarbonyl compound.

According to the present invention, the desired
10 optically active 1,3-syn-diol compound of the formula (VI) can be synthesized in good yield and at a high syn-selectivity by reducing the 1,3-dicarbonyl compound of the formula (V) by a simple operation by means of the optically active β -aminoalkoxyborane complex of the
15 formula (I). The optically active 1,3-syn-diol constitutes an important partial structure of an antihyperlipemia therapeutic agent (a HMG-CoA reductase inhibitor). Thus, the optically active β -aminoalkoxyborane complex (I) of the present invention is
20 useful for the production of such a typical HMG-CoA reductase inhibitor as Lovastatin, Simvastatin or Pravastatin. Further, the compound of the present invention is applicable to various carbonyl compounds (of the formula (III)) to produce optically active alcohol
25 compounds (of the formula (IV)) in good asymmetric yield.

Now, the present invention will be described in further detail with reference to Examples. However, it

- 65 -

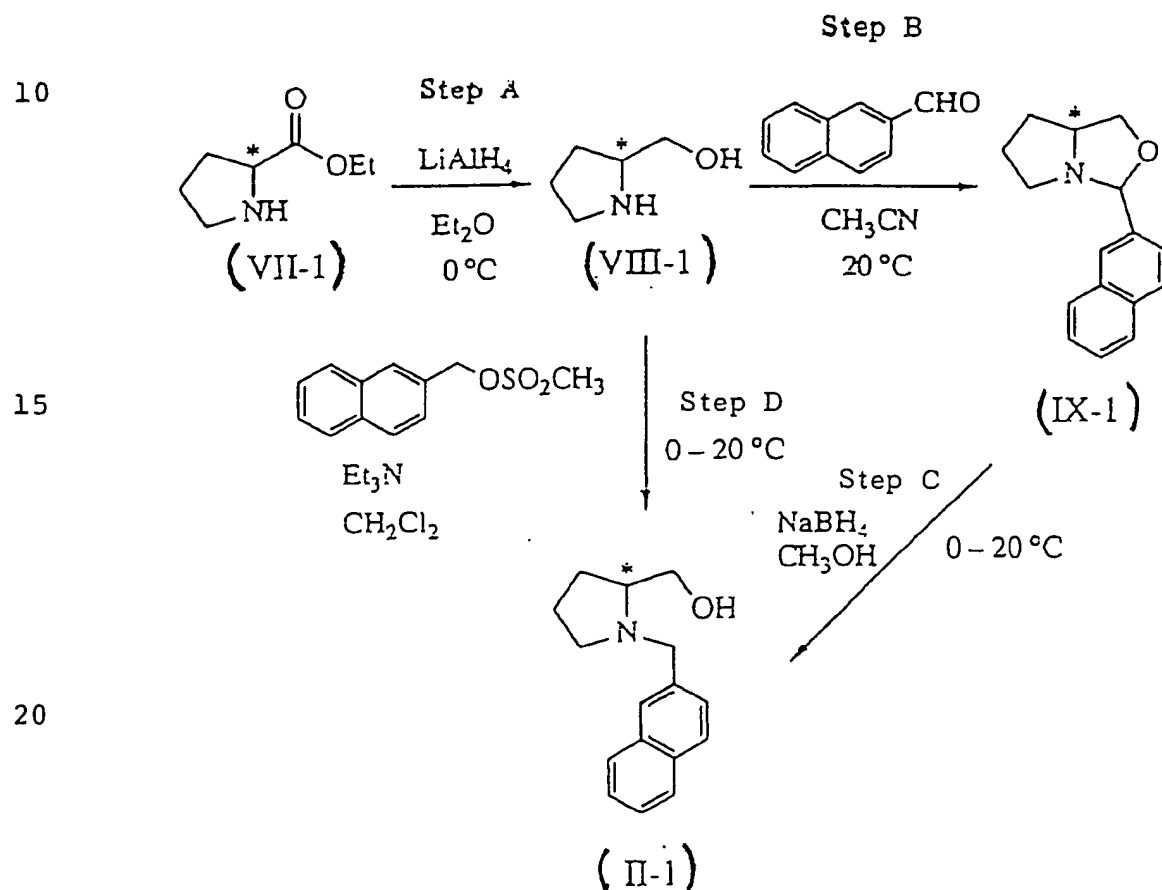
should be understood that the present invention is by no means restricted to such specific Examples.

EXAMPLE 1

Preparation of the optically active β -aminoalcohol

5 compound (II) (Steps A, B and D)

Preparation of (S)-N-(β -naphthyl)methyl-2-pyrrolidine
methanol ((S)-II-1)

25 Step A

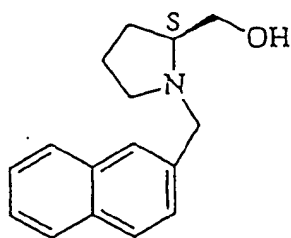
Commercially available proline ethyl ester (VII-1) was reduced in ethyl ether under cooling with ice by

- 66 -

means of lithium aluminum hydride to obtain prolinol (VIII-1). Using optically active starting materials, the corresponding optically active prolinols (VIII-1) were obtained, respectively.

5 Steps B and C

1.000 g (9.89 mmol) of (S)-prolinol ((S)-(VIII-1)) was dissolved in 25 ml of dry acetonitrile, and 1.545 g (9.89 mmol) of β -naphthoaldehyde was added thereto with stirring. The mixture was stirred for 24 hours. Then, acetonitrile was distilled off under reduced pressure to obtain an oxazolidine compound ((S)-(IX-1) (crude product: 2.55 g) quantitatively. Further, this oxazolidine compound was dissolved in 20 ml of methanol and cooled with ice. Then, 374 mg (9.89 mmol) of sodium borohydride was added thereto, and the mixture was stirred for 4 hours. Then, methanol was distilled off under reduced pressure, and the residue was recrystallized from chloroform to obtain S-N-(β -naphthyl)methyl-2-pyrrolidine methanol ((S)-II-1) (2.40 g) quantitatively.



((S)-II-1)

25

$[\alpha]_D^{20} -49.8^\circ$ (C=0.1, CH₃OH)

- 67 -

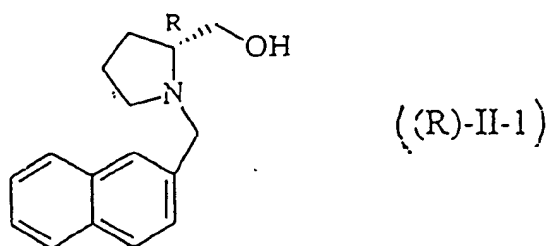
IR spectrum (KBr) ν_{\max} cm^{-1} : 3200, 3030, 2950, 2850, 1600, 1580, 1420, 1340, 1180, 1020, 850, 820, 740

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 7.30-7.83 (7H, m, aromatic-H), 2.28-4.23 (8H, m, other-H), 1.66-1.90 (4H, m, $\text{C-CH}_2\text{CH}_2\text{-C}$)

5 Preparation of (R)-N-(β -naphthyl)methyl-2-pyrrolidine methanol ((R)-II-1)

Using (R)-prolinol ((R)-VIII-1) as the starting material, a similar operation was carried out to obtain R-N-(β -naphthyl)methyl-2-pyrrolidine methanol ((R)-II-1).

10



15

$[\alpha]_{\text{D}}^{20} +50.7^\circ$ ($\text{C}=0.1$, CH_3OH)

IR spectrum (KBr) ν_{\max} cm^{-1} : 3200, 3030, 2950, 2850, 1600, 1580, 1420, 1340, 1180, 1020, 850, 820, 740

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 7.30-7.83 (7H, m, aromatic-H), 2.28-4.23 (8H, m, other-H), 1.66-1.90 (4H, m, $\text{C-CH}_2\text{CH}_2\text{-C}$)

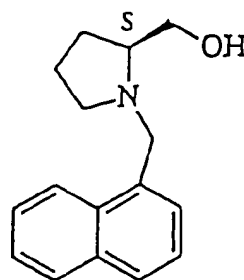
20

Preparation of (S)-N-(α -naphthyl)methyl-2-pyrrolidine methanol ((S)-II-2)

Using (S)-prolinol ((S)-VIII-1) and α -naphthoaldehyde as the starting materials, a similar operation was carried out to obtain (S)-N-(α -naphthyl)methyl-2-pyrrolidine methanol ((S)-II-2).

25

- 68 -



((S)-II-2)

5

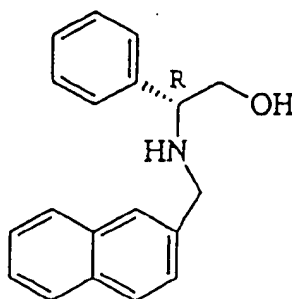
$[\alpha]_D^{20} -65.6^\circ$ (C=0.16, CH₃OH)

IR spectrum (NaCl) ν_{max} cm⁻¹: 3400, 3040, 2950, 2870, 1600, 1500, 1460, 1350, 1170, 1040, 800, 790, 780

¹H-NMR(CDCl₃) δ ppm: 7.25-8.30 (7H, m, aromatic-H), 2.60-4.55 (7H, m, other
10 -H), 2.35 (1H, br, OH), 1.65-2.01 (4H, m, C-CH₂CH₂-C)

Preparation of (R)-N-(β -naphthyl)methyl-2-phenylglycinol
((R)-II-3)

Using 1.00 g (7.29 mmol) of (R)-phenylglycinol ((R)-
15 VIII-2) and β -naphthoaldehyde, a similar operation was
carried out to obtain (R)-N-(β -naphthyl)methyl-2-
phenylglycinol (2.01 g) ((R)-II-3) quantitatively.



((R)-II-3)

20

$[\alpha]_D^{20} +3.1^\circ$ (C=0.1, CH₃OH)

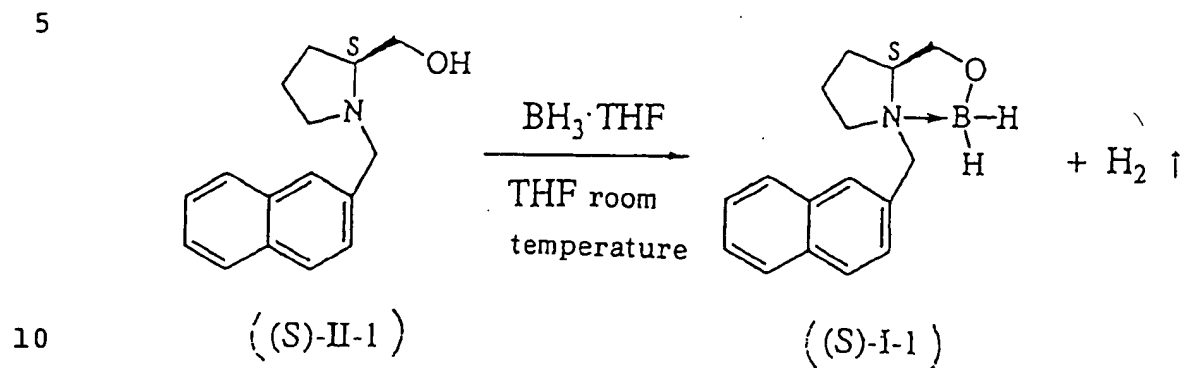
¹H-NMR(CDCl₃) δ ppm: 7.30-7.80 (12H, m, aromatic-H), 3.50-4.30 (5H, m, othe
25 r-H), 2.30 (1H, br, OH), 2.02 (1H, br s, NH)

EXAMPLE 2

- 69 -

Preparation of the optically active β -aminoalkoxyborane complex (I) (Step E)

Preparation of (S)-N-(β -naphthyl)methyl-2-pyrrolidine methoxyborane ((S)-I-1)



2.41 g (10 mmol) of (S)-N-(β -naphthyl)methyl-2-pyrrolidine methanol ((S)-II-1) was dissolved in 50 ml of dry THF, and 10 ml of a tetrahydrofuran solution

15 containing 1.0M of a borane·tetrahydrofuran complex (hereinafter referred to simply as a $\text{BH}_3 \cdot \text{THF}$ solution) was dropwise added thereto with stirring. After termination of generation of hydrogen gas, the mixture was further stirred for 10 minutes. This borane complex

20 was used in the form of the THF solution for reduction of carbonyl compounds. Further, THF was distilled off at room temperature under reduced pressure to obtain 2.53 g (100%) of the desired substance as a viscous oily substance. The physical property values of this

25 substance are as follows:

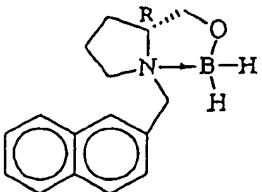
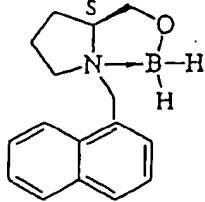
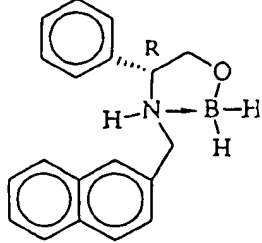
- 70 -

IR spectrum (KBr) ν_{\max} cm^{-1} : 3030, 2950, 2850, 2350 (B-H), 1600, 1450, 1420, 1360, 1280, 1180, 1030, 850, 820, 750

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 7.30-7.83 (7H, m, aromatic-H), 1.00-5.80 (13H, m, other-H)

- 5 Using compounds ((R)-II-1), ((S)-II-2) and ((R)-II-3) as starting materials, similar operations were carried out to obtain optically active β -aminoalkoxyborane complexes (I) as identified in Table 2.

Table 2

Structure	Chemical name
	(R)-[N-(β -naphthyl)methyl]-pyrrolidine methoxyborane [(R)-I-1]
	(S)-[N-(β -naphthyl)methyl]-pyrrolidine methoxyborane [(S)-I-2]
	(R)-[N-(β -naphthyl)methyl]-phenylethoxyborane [(R)-I-3]

REFERENCE EXAMPLE 1

Preparation of ethyl (E)7-[2'-cyclopropyl-4'-(p-

- 71 -

fluorophenyl)quinolin-3'-yl]-3,5-dioxo-6-heptenoate

Under a nitrogen stream, 2.35 g (63.1 mmol) of 60% sodium hydride was suspended in 300 ml of dry THF, and the suspension was stirred for 5 minutes and then cooled
5 with ice. Then, 7.47 g (57.4 mmol) of ethyl acetoacetate was gradually dropwise added by an injector, and after termination of generation of hydrogen, the mixture was stirred for 15 minutes. Then, 37.8 ml (60.3 mmol) of 1.6M n-butyl lithium was gradually
10 dropwise added thereto by an injector, and the mixture was stirred for 15 minutes. After confirming that the color of the reaction solution turned to yellow to orange red, 6.00 g (15.9 mmol) of (E)3-[2'-cyclopropyl-4'-(p-fluorophenyl)quinolin-3'-yl]-2-propenoic acid-N-methyl-N-
15 methoxyamide (G. B. Reddy, T. Minami, T. Hanamoto, T. Hiyama, J. Org. Chem., 56, 5754, 1991) was dissolved in 100 ml of dry THF, and the solution was dropwise added to the reaction solution. Then, the reaction temperature was raised to room temperature, and the mixture was
20 stirred for 24 hours. The reaction solution was cooled with ice, and the reaction was terminated by an addition of 200 ml of a 1M acetic acid aqueous solution. The aqueous layer was separated and extracted twice with 200 ml of ethyl acetate. The extract was put into the
25 organic layer, and the mixture was washed twice with 50 ml of a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the

- 72 -

solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate = 10/1) and then recrystallized from ethyl acetate to obtain 3.11 g of the above-identified compound.

MS spectrum (EI)m/e: 445 (M⁺), 400, 358, 330, 316, 288

¹H-NMR (CDCl₃) δ ppm : 7.97-7.19 (8H, m, aromatic-H), 7.71 (1H, d, J=16Hz, COCH=C), 6.03 (1H, d, J=16Hz, COC=CH), 5.51 (1H, s, enol-olefinic-H), 4.21 (2H, q, J=7Hz, COOCH₂), 3.40 (2H, s, COCH₂COO), 2.35-2.40 (1H, m, CH-c-propyl), 1.39-1.41, 1.07-1.09 (4H, m, -CH₂CH₂-), 1.28 (3H, t, J=7Hz, COOCCCH₃)

EXAMPLE 3

Catalytic asymmetric reduction of a monocarbonyl compound by means of the optically active N-naphthylmethyl-2-pyrrolidine methanol (compound (II)/BH₃)

15 A carbonyl compound (1 mmol) was dissolved in 5 ml of THF, and 192 mg (6 mmol) of methanol and 23 mg (0.1 mmol) of the optically active N-naphthylmethyl-2-pyrrolidine methanol (compound (II)) were added thereto. Then, 3 ml or 10 ml (3 mmol or 10 mmol) of a 1M BH₃·THF solution was added thereto, and the mixture was stirred under a temperature condition of 20°C or 30°C for from 6 to 19 hours. To the reaction solution, 13 ml of 1N HCl was added for salting out, followed by extraction with 100 ml of ethyl acetate. Then, the extract was washed with 10 ml of a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure, and the

- 73 -

obtained liquid was purified by a thin layer chromatography for separation to obtain the desired optically active alcohol quantitatively.

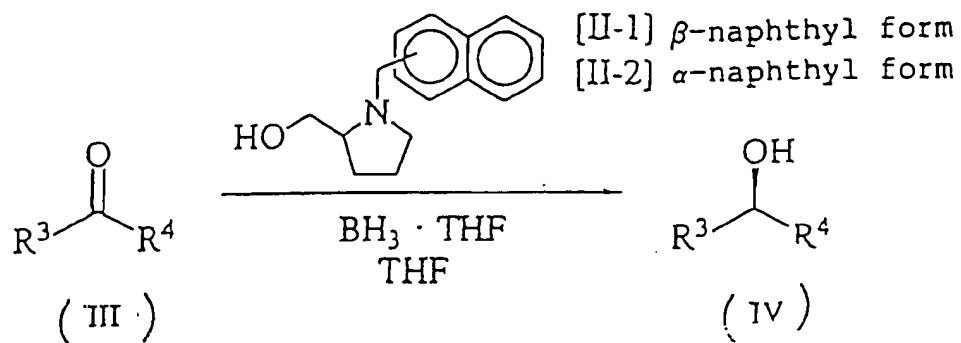
Table 3 shows the results of asymmetric reduction of various monocarbonyl compounds using the optically active N-naphthylmethyl-2-pyrrolidine methanol (compound (II-1) or compound (II-2)). The asymmetric yield and the absolute configuration of the obtained alcohol were determined by comparison with an optically active standard product by converting the alcohol product to a urethane diastereomer, followed by high performance liquid chromatography using silica gel in accordance with a high performance liquid chromatography analysis using a CHIRALCEL OD column by Daicel Chemical Industries, Ltd. or the method by Lamed et al. (E. Keinan, E. K. Hafeli, K. K. Seth, and R. Lamed, J. Am. Chem. Soc., 108, 162 (1986)).

20

25

- 74 -

Table 3



Test No.	Carbonyl compound	Compound (II) (mol times)	Chemical yield (%)	Asymmetric yield (%)	Absolute configur- ation
1		[(S)-II-1] 0.1	94 ^{a)}	100	S
2		[(S)-II-2] 0.1	91 ^{a)}	100	S
3		[(S)-II-2] 0.1	94 ^{a)}	70	—
4		[(S)-II-1] 0.002	100 ^{b)}	46	R
5		[(S)-II-1] 0.02	100 ^{b)}	99	R
6		[(S)-II-1] 0.05	100 ^{b)}	99	R
7		[(S)-II-1] 0.2	100 ^{b)}	99	R

a) Reaction temp.: 30°C, Reaction time: 6 hrs, $\text{BH}_3 \cdot \text{THF}$: 10 mmolb) Reaction temp.: 20°C, Reaction time: 19 hrs, $\text{BH}_3 \cdot \text{THF}$: 3 mmol

- 75 -

The compound (I) of the present invention presented a high asymmetric yield in a catalytic amount in the asymmetric reduction of a monocarbonyl compound (III), without isolation i.e. as formed in the reaction system by the compound (II). In the case of conventional asymmetric reduction using 2-hexanone as the substrate (J. Chem. Soc. Perkin Trans. I. 2887 (1984), J. Org. Chem. 49, 555 (1984)), even when a borane complex was used in a stoichiometric amount, the asymmetric yield was only 25% (a borane complex having a polymer substituent introduced on the nitrogen of (S)-proline) or 55% (a (S)-2-amino-3-methyl-1,1-diphenylbutan-1-ol borane complex). Thus, the superiority of the compound of the present invention was proved.

15 EXAMPLE 4

Asymmetric reduction of a 1,3-dicarbonyl compound (V) by various optically active β -aminoalkoxyborane complexes (I)

1 mmol (445.5 mg) of a 1,3-dicarbonyl compound (V) was dissolved in 30 ml of THF, and 1 ml of a THF solution of 1.0M diethylmethoxyborane·THF or 1 mmol (204.3 mg) of aluminum tri-*i*-propoxide was added thereto with stirring. The mixture was adjusted to -78°C or 20°C under a nitrogen gas stream.

25 To this 1,3-dicarbonyl compound (V) solution, the (S)-N-(β -naphthyl)methyl-2-pyrrolidine methoxyborane complex ((S)-I-1) obtained in Example 2 was dropwise

- 76 -

added, and the mixture was stirred for 3 hours.

Otherwise, to form the borane complex in the reaction system, from 2 to 10 ml (2 to 10 mmol) of a 1.0M $\text{BH}_3 \cdot \text{THF}$ solution was dropwise added to the (S)-N-(β -
5 naphthyl)methyl-2-pyrrolidine methanol ((S)-I-1) obtained in Example 1 or a THF solution of various optically active β -aminoalcohol (0.1 to 3 mmol). This solution is dropwise added to the above 1,3-dicarbonyl compound (V), and the mixture was stirred for from 3 to 28 hours. In
10 the case where a catalytic amount of β -aminoalcohol is employed, 192 mg (6 mmol) of methanol was further added.

Then, acetic acid (9 mmol, 540.5 mg) was added to the reaction solution, and the mixture was diluted with 300 ml of ethyl acetate, washed with 20 ml of a saturated
15 sodium chloride aqueous solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and 1 ℓ of methanol was added to the orange red liquid thereby obtained, and the mixture was heated at a temperature of from 50 to 60°C for one hour.
20 Then, methanol was distilled off under reduced pressure. The obtained yellow liquid was purified by silica gel column chromatography to obtain the desired optically active 1,3-syn-diol compound (VI-1). The determination of the asymmetric yield (%ee) was conducted by high
25 performance liquid chromatography using CHIRALCEL OD column, manufactured by Daicel Chemical Industries, Ltd.

With respect to the reducing agents shown in Table 4,

- 77 -

the β -aminoalkoxyborane complex ((S)-I-1) was used in Test Nos. 1 to 3. In Test Nos. 4 to 9, the β -aminoalkoxyborane complex formed in the reaction system by β -aminoalcohol, was used. In Test No. 5 and 6, a catalytic amount of β -aminoalcohol ((S)-II-1) was used. Further, in Test No. 6, dichloromethane was used as the solvent.

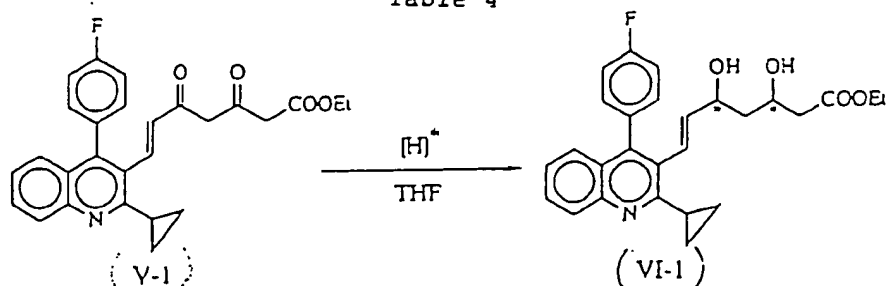
10

15

20

25

Table 4



No.	Reducing agent	Metal reagent	Chemical yield (%)	syn-forming rate (%) (syn/syn+anti)	Asymmetric yield (%ee)	Absolute configuration
1	[(S)-I-1] 3 molar times	Et ₂ BOMc	42 ^{a)}	99	100	3S, 5R
2	[(S)-I-1] 3 molar times	Et ₂ BOMc	53 ^{b)}	94	100	3S, 5R
3	[(S)-I-1] 3 molar times	—	51 ^{a)}	95	100	3S, 5R
4	[(S)-II-1] + BH ₃ 3 molar times each	Et ₂ BOMc	50 ^{b)}	95	100	3S, 5R
5	[(S)-II-1] 0.1 molar time + BH ₃ 10 molar times	Et ₂ BOMc	33 ^{c)}	94	91	3S, 5R
6	[(S)-II-1] 0.25 molar time + BH ₃ 10 molar times	Et ₂ BOMc	13 ^{d)}	95	94	3S, 5R
7	[(R)-II-3] + BH ₃ 2 molar times each	Et ₂ BOMc	19 ^{a)}	100	24	3R, 5S
8	[(R)-II-1] + BH ₃ 2 molar times each	Al(OPr-i) ₃	15 ^{e)}	99	100	3R, 5S
9	[(R)-II-1] + BH ₃ 3 molar times each	Al(OPr-i) ₃	74 ^{f)}	99	100	3R, 5S

a) Reaction temp.: -78°C, Reaction time: 3 hrs

b) Reaction temp.: 20°C, Reaction time: 3 hrs

c) Reaction temp.: 20°C, Reaction time: 28 hrs

d) Reaction temp.: -78°C, Reaction time: 23 hrs, CH₂Cl₂ solvent

e) Reaction temp.: -78°C, Reaction time: 5 hrs

f) Reaction temp.: 20°C, Reaction time: 20 hrs

- 79 -

COMPARATIVE EXAMPLE 1

Using conventional borane complexes, the operation was conducted in the same manner as in Example 4. The results are shown in Table 5.

5

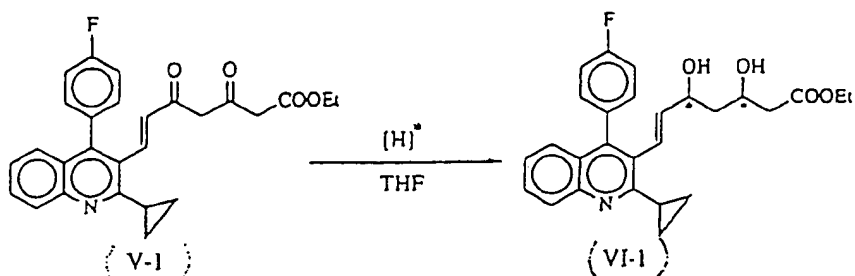
10

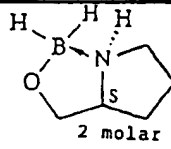
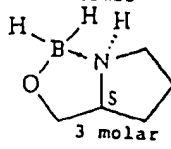
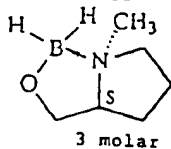
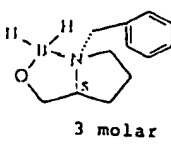
15

20

25

Table 5



Test No.	Reducing agent	Borane reagent Et ₂ BOMe	Chemical yield (%)	syn-forming rate (%) (syn/syn+anti)	Asymmetric yield (%ee)	Absolute configuration
1	 2 molar times	—	78 ^{a)}	60	21	3S, 5R
2	 3 molar times	1 eq	65 ^{a)}	82	23	3S, 5R
3	 3 molar times	1 eq	68 ^{a)}	43	14	3S, 5R
4	 3 molar times	1 eq	28 ^{b)}	33	6	3S, 5R

a) Reaction temp.: -78°C, Reaction time: 3 hrs

b) Reaction temp.: 20°C, Reaction time: 3 hrs

- 81 -

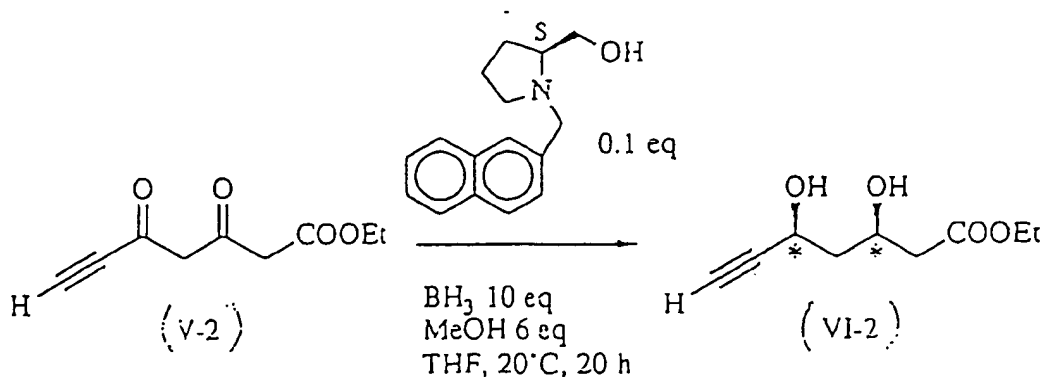
EXAMPLE 5

50 mg (0.27 mmol) of ethyl 3,5-dioxo-6-heptynoate was dissolved in 5 ml of THF and 52 ml of methanol. Then, with or without addition of aluminum tri-*i*-propoxide as a metal reagent, a reaction was conducted at 20°C for 20 hours using 5.4 ml of a 1.0M $\text{BH}_3 \cdot \text{THF}$ solution and 6.2 mg (0.027 mmol) of the (S)-N-(β -naphthyl)methyl-2-pyrrolidine methanol (compound (S)-II-1) obtained in Example 1, to obtain ethyl 3,5-dihydroxy-6-heptynoate (VI-2) as oily desired product.

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 4.81 (1H, br, $=\text{CH-OH}$), 4.17 (2H, q, $J=7\text{Hz}$, COOCH_2), 3.60 (1H, m, C-CH(OH)-C), 3.04 (1H, s, $\text{C}\equiv\text{C-H}$), 1.50-1.65 (6H, m, other-H), 1.3 (3H, t, $J=7\text{Hz}$, $\text{COOCH}_2\text{CH}_3$).

IR (NaCl) cm^{-1} : 3400 (OH), 2220 ($\text{C}\equiv\text{C}$), 1720 (C=O).

Table 6



No.	Metal reagent	Chemical yield (%)	syn-forming rate (%) (syn/syn+anti)	Asymmetric yield (%ee)	Absolute configuration
1	—	90	99	82	3R, 5S
2	$\text{Al}(\text{OPr}^i)_3$	91	99	100	3R, 5S

- 82 -

The compound of the present invention presented a higher asymmetric yield and a higher diastereo-selectivity (higher syn-formation rate) than conventional borane complex catalysts, in a catalytic amount, in the asymmetric reduction of 1,3-dicarbonyl compounds (V-1) and (V-2).

10

15

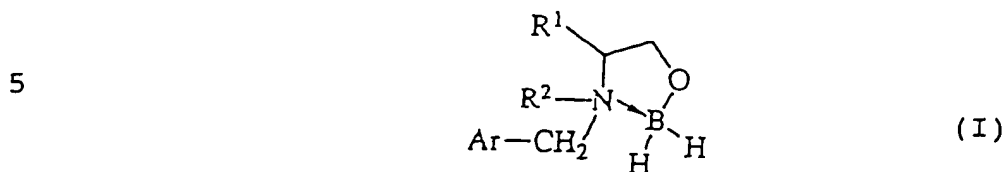
20

25

- 83 -

CLAIMS:

1. An optically active β -aminoalkoxyborane complex of the formula (I):

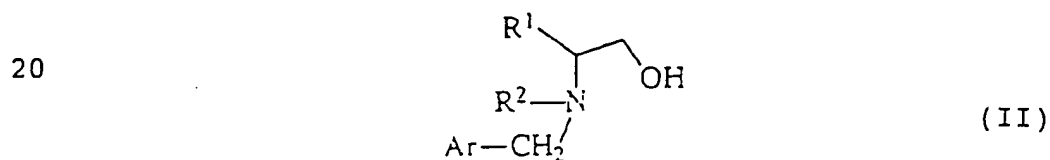


wherein R^1 is C_1 - C_8 alkyl, C_3 - C_7 cycloalkyl, C_7 - C_{11} aralkyl or C_6 - C_{10} aryl, R^2 is hydrogen, C_1 - C_8 alkyl, C_3 - C_7 cycloalkyl or C_7 - C_{11} aralkyl, or R^1 and R^2 together form $(CH_2)_n$ wherein n is 3 or 4, and Ar is naphthyl, anthryl or phenanthryl, which may be substituted by from 1 to 3 substituents selected from the group consisting of halogen, nitro, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_7 - C_{11} aralkyl, C_6 - C_{10} aryl, C_1 - C_6 alkoxy and styrene polymer substituents.

10

15

2. An optically active β -aminoalcohol compound of the formula (II):



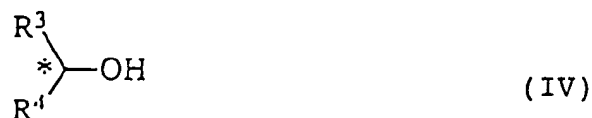
wherein R^1 is C_1 - C_8 alkyl, C_3 - C_7 cycloalkyl, C_7 - C_{11} aralkyl or C_6 - C_{10} aryl, R^2 is hydrogen, C_1 - C_8 alkyl or C_7 - C_{11} aralkyl, or R^1 and R^2 together form $(CH_2)_n$ wherein n is 3 or 4, and Ar is naphthyl, anthryl or phenanthryl, which may be substituted by from 1 to 3 substituents

25

- 84 -

selected from the group consisting of halogen, nitro, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₁ aralkyl, C₆-C₁₀ aryl, C₁-C₆ alkoxy and styrene polymer substituents.

- 5 3. A process for producing an optically active β -aminoalkoxyborane complex of the formula (I) as defined in Claim 1, which comprises reacting an optically active β -aminoalcohol compound of the formula (II) as defined in Claim 2, with a borane reagent.
- 10 4. A process for producing an optically active alcohol compound of the formula (IV):



15

wherein R³ and R⁴ differ from each other and represent C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkenyl, C₇-C₁₁ aralkyl, and C₆-C₁₄ aryl, or R³ and R⁴ together form a cyclic structure, and

- 20 * indicates an optically active center, which comprises reducing a carbonyl compound of the formula (III):

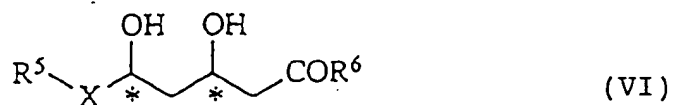


25

wherein R³ and R⁴ are as defined above, with an optically active β -aminoalkoxyborane complex as defined in Claim 1.

- 85 -

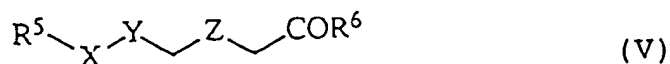
5. A process for producing a compound of the formula (VI).



wherein when X is a bond, R⁵ is CHO, CH(OR⁹)(OR¹⁰)
 (wherein each of R⁹ and R¹⁰ which are independent of each
 other, is hydrogen or C₁-C₃ alkyl, or R⁹ and R¹⁰ together
 10 form C₂-C₅ alkylene), CH₂OR¹¹ (wherein R¹¹ is hydrogen,
 C₁-C₃ alkyl, benzyl which may be substituted by methyl or
 methoxy, trityl, tetrahydropyranyl, methoxymethyl,
 trimethylsilyl, dimethyl-tert-butylsilyl or diphenyl-
 tert-butylsilyl), CH₂R¹² (wherein R¹² is fluoro, chloro,
 15 bromo or iodo), CN, CO₂R¹³ (wherein R¹³ is hydrogen, C₁-C₄
 alkyl, or benzyl which may be substituted by methyl or
 methoxy), or CONR¹⁴R¹⁵ (wherein each of R¹⁴ and R¹⁵ which
 are independent of each other, is hydrogen, C₁-C₃ alkyl,
 benzyl, 1-methylbenzyl, or phenyl which may be
 20 substituted by methyl or methoxy), and when X is -CH₂-,
 -CH₂CH₂-, -CH=CH-, -(CH₃)C=CH-, -CH=C(CH₃)- or -C≡C-, R⁵
 is hydrogen, trialkylsilyl, a carbon ring aliphatic
 group, a carbon ring aromatic group, a heterocyclic
 aromatic group, a condensed heterocyclic aromatic group,
 25 a chain unsaturated aliphatic group or a cyclic
 unsaturated aliphatic group, and R⁶ is hydroxyl, C₁-C₁₀
 alkoxy, OM (wherein M is lithium, sodium, potassium,

- 86 -

calcium, NHR'_3 (wherein R' is hydrogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{C}_2\text{-C}_5$ alkenyl, phenyl or benzyl)) or $\text{C}_0\text{-C}_7$ amino, and $*$ is an optically active center, provided that the two optically active centers take a syn conformation to each other, which comprises reducing a carbonyl compound of the formula (V):



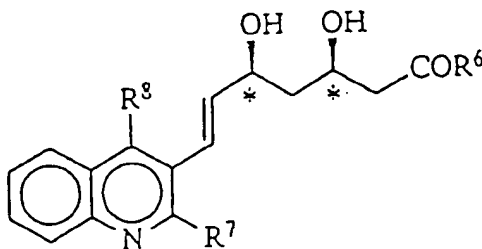
10

wherein R^5 , R^6 and X are as defined above, and each of Y and Z which are independent of each other, is -CO- or -CH(OH)- , provided that Y and Z are not simultaneously -CH(OH)- , with an optically active β -aminoalkoxyborane complex as defined in Claim 1.

15

6. A process for producing a compound of the formula (VI-1):

20



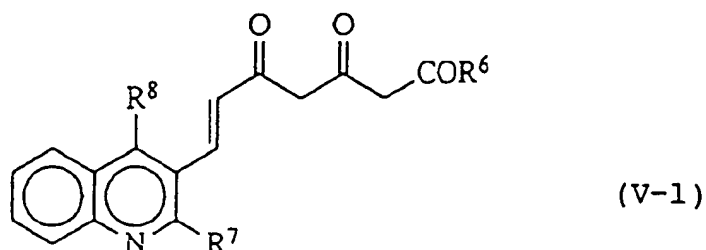
(VI-1)

wherein R^6 is hydroxyl, $\text{C}_1\text{-C}_{10}$ alkoxy, OM (wherein M is lithium, sodium, potassium, calcium, NHR'_3 (wherein R' is hydrogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{C}_2\text{-C}_5$ alkenyl, phenyl or benzyl)) or $\text{C}_0\text{-C}_7$ amino, R^7 is $\text{C}_1\text{-C}_7$ alkyl or $\text{C}_3\text{-C}_7$ cycloalkyl, R^8 is phenyl which may be substituted

25

- 87 -

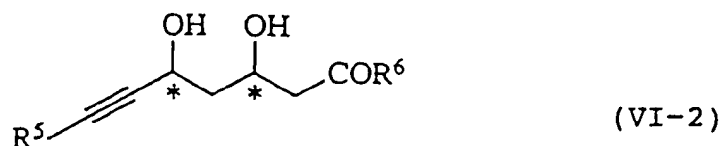
by C₁-C₇ alkyl, fluoro, chloro or bromo, * indicates an optically active center, provided that the two optically active centers take a syn conformation to each other, which comprises reducing a 1,3-dicarbonyl compound of the formula (V-1):



10

wherein R⁶, R⁷ and R⁸ are as defined above, with an optically active β-aminoalkoxyborane complex as defined in Claim 1.

7. A process for producing an optically active 1,3-syn-diol compound of the formula (VI-2):



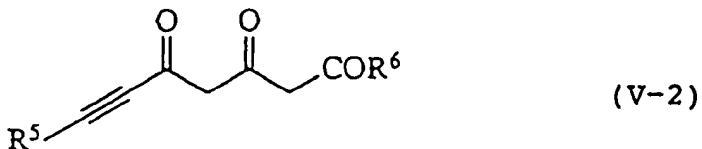
20 wherein R⁵ is hydrogen, trialkylsilyl, a carbon ring aliphatic group, a carbon ring aromatic group, a heterocyclic aromatic group, a condensed heterocyclic aromatic group, a chain unsaturated aliphatic group or a cyclic unsaturated aliphatic group, R⁶ is hydroxyl, C₁-C₁₀ alkoxy, OM (wherein M is lithium, sodium, potassium, calcium, NHR'₃ (wherein R' is hydrogen, C₁-C₃ alkyl, C₃-C₇ cycloalkyl, C₂-C₅ alkenyl, phenyl or benzyl)) or C₀-C₇

25

- 88 -

amino, and * indicates an optically active center,
provided that the two optically active centers take a syn
conformation to each other, which comprises reducing a
1,3-dicarbonyl compound of the formula (V-2):

5



wherein R⁵ and R⁶ are as defined above, with an optically
10 active β -aminoalkoxyborane complex as defined in Claim 1.

15

20

25

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/JP 94/00056

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 5 C07F5/02 C07C215/28 C07D207/08 C07C29/143 C07D215/14
 C07B53/00 C07B41/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 5 C07B C07C C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 5, 3 August 1987, Columbus, Ohio, US; abstract no. 39327q, CEGLA, M. 'CHIRAL N-(ARYLALKYL)-2-AMINO-1-BUTANOL DERIVATIVES AS STEREoselective REDUCTION AGENTS OF KETONES' page 654 ; see abstract & POL. J. CHEM. vol. 59, no. 10 , 1986 pages 1265 - 1267	2
A	---	1,3-7
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

2 March 1994

Date of mailing of the international search report

15. 03. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+ 31-70) 340-3016

Authorized officer

Rinkel, L

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 94/00056

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON vol. 14 , 1961 pages 284 - 287 GOVINDACHARI, T.R. ET AL. 'CHEMICAL EXAMINATION OF TYLOPHORA ASTHMATICA-IV. SYNTHESIS OF TYLOPHORINE' * compound II*	2
X	--- CHEMICAL ABSTRACTS, vol. 74, no. 3, 18 January 1971, Columbus, Ohio, US; abstract no. 13313g, CHAUNCY, B. ET AL. 'SYNTHESIS OF PHENANTHROINDOLIZIDINES. II. SYNTHESIS OF (+)-TYLOCREBINE, (+)-TYLOPHORINE), (+)-ANTOFINE, AND (+)-2,3-DIMETHOXYPHENANTHROINDOLIZIDINE' page 326 ; see abstract & AUST. J. CHEM. vol. 23, no. 12 , 1970 pages 2503 - 2516	2
X	--- CHEMICAL ABSTRACTS, vol. 70, no. 19, 12 May 1969, Columbus, Ohio, US; abstract no. 88024q, CHAUNCY, B. ET AL. 'SYNTHESIS OF PHENANTHROINDOLIZIDINE' page 368 ; see abstract & AUST. J. CHEM. vol. 22, no. 2 , 1969 pages 427 - 429	2
X	--- CHEMICAL ABSTRACTS, vol. 110, no. 5, 30 January 1989, Columbus, Ohio, US; abstract no. 38872p, HASHIZUME, H. ET AL. 'RESOLUTION OF D,L-PANTOLACTONE' page 531 ; see abstract & JP,A,63 139 179 (FUJI PHARMACEUTICAL INDUSTRIES CO., LTD.) 10 June 1988	2
A	--- EP,A,0 453 288 (MERCK & CO. INC.) 23 October 1991 see the whole document	1,3-7
A	--- EP,A,0 171 175 (SUMITOMO CHEMICAL INDUSTRIES LTD.) 12 February 1986 see the whole document --- -/--	1,3-7

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 94/00056

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TETRAHEDRON LETTERS vol. 29, no. 26 , 1988 pages 3201 - 3204 COREY, E.J. ET AL. 'ENANTIOSELECTIVE ROUTE TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF GINKGOLIDE B' cited in the application ---</p>	
A	<p>TETRAHEDRON LETTERS vol. 29, no. 49 , 1988 pages 6467 - 6470 HANAMOTO, T. ET AL. 'A FACILE ENTRY TO .BETA.,.DELTA.-DIKETO AND SYN-.BETA.,.DELTA.-DIHYDROXY ESTERS' cited in the application -----</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 94/00056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP-A-63139179	10-06-88	NONE	
EP-A-0453288	23-10-91	US-A- 5157129	20-10-92
		JP-A- 4224581	13-08-92
EP-A-0171175	12-02-86	JP-B- 5001273	07-01-93
		JP-A- 61018790	27-01-86
		CA-A- 1250589	28-02-89
		US-A- 4923999	08-05-90
		US-A- 4749809	07-06-88